STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 166476

TO: Michael Meller **Location: REM-3C18** **Art Unit: 1655** **September 21, 2005** **Case Serial Number: 09/985699**	**From: P. Sheppard** **Location: Remsen Building** **Phone: (571) 272-2529** **sheppard@uspto.gov**

Search Notes

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Access DB# 11e1476

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Michael Meller Examiner #: 69404 Date: 9/21/05
Art Unit: 1655 Phone Number ~~571-272-0967~~ Serial Number: 09/985,699
Mail Box and Bldg/Room Location: Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: therapeutic Agent.

Inventors (please provide full names): Mark Pepys

Paula

Earliest Priority Filing Date: 8/9/01

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please Search the claims in the PG Pub Database.

C-Chen

Rush

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SEP 21 2005
TECH/CHEM. DIVS.
(STIC)

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STAFF USE ONLY

Searcher: Sheppard

Type of Search

NA Sequence (#)_____

Vendors and cost where applicable

STN _____

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I. AMENDMENT

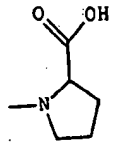
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1-17. (Canceled)

18. (Currently amended) A method for the depletion of ~~a disease-associated protein population~~ serum amyloid P component (SAP) from the plasma of a subject in need of such treatment, which comprises:

(a) administering to the subject a therapeutically effective amount of a ~~non-proteinaceous agent, which agent comprises a plurality of ligands covalently co-linked to permit complexation with a plurality of the disease-associated proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins~~ D-proline of the formula (R)-1-[6-(R)-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid or a pharmaceutically acceptable salt or mono- or diester thereof, wherein R is the group



;

(b) binding of at least two ~~of the~~ ligands of said D-proline by ~~the~~ ligand binding sites of ~~the~~ SAP proteins in the plasma;

(c) forming thereby a complex between ~~the agent~~ said D-proline and a plurality of ~~the~~ SAP proteins, wherein the complex is abnormal to the subject; and

(d) causing the complex to be identified by the physiological mechanisms of the subject and cleared from the plasma; and

(e) monitoring the clearance of ~~the disease-associated protein population~~ SAP from the subject's plasma.

19-23. (Canceled)

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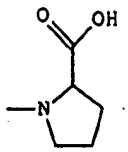
24. (Currently amended) A method for the depletion of a ~~disease-associated protein population~~ SAP from the plasma of a subject in need of such treatment, which comprises administering to the subject a therapeutically effective amount of ~~a non-proteinaceous agent, which agent has the general structure Ligand-linker-Ligand and is capable of forming a complex with a plurality of the disease-associated proteins in the presence thereof, wherein the ligands are the same or different and are capable of being bound by ligand-binding sites present on the proteins~~ D-proline of the formula (R)-1-[6-(R)-2-Carboxy-pyrrolidin-l-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid or a pharmaceutically acceptable salt or mono- or diester thereof, wherein R is the group



and monitoring the clearance of the disease-associated protein population from the subject's plasma.

25-47. (Canceled)

New claims:

48. (New) The method of claim 18, wherein said D-proline is administered orally with a dosage of 50 to 500 mg/per day.

49. (New) The method of claim 18, wherein said D-proline is administered by injection with a dosage of 0.05 to 6 mg/kg/day.

50. (New) The method of claim 49, wherein said D-proline is administered by injection with a dosage of 0.1 to 6 mg/kg/day.

51. (New) The method of claim 50, wherein said D-proline is administered by injection with a dosage of 0.25 to 6 mg/kg/day.

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52. (New) The method of claim 24, wherein said D-proline is administered orally with a dosage of 50 to 500 mg/per day.

53. (New) The method of claim 24, wherein said D-proline is administered by injection with a dosage of 0.05 to 6 mg/kg/day.

54. (New) The method of claim 53, wherein said D-proline is administered by injection with a dosage of 0.1 to 6 mg/kg/day.

55. (New) The method of claim 54, wherein said D-proline is administered by injection with a dosage of 0.25 to 6 mg/kg/day.

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L20         538 SEA SSS FUL L18
     FILE 'HCAPLUS' ENTERED AT 15:44:19 ON 21 SEP 2005
L24         305 SEA ABB=ON  PLU=ON  L20
L25       12939 SEA ABB=ON  PLU=ON  SERUM(W)AMYLOID(W)(P OR PROTEIN) OR SAP
L26           5 SEA ABB=ON  PLU=ON  L24 AND L25
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L37           3 SEA ABB=ON  PLU=ON  (L36 AND L25) NOT (L26 OR L31)
                D STAT QUE
                D IBIB ABS HITSTR L37 1-3
L38          29 SEA ABB=ON  PLU=ON  (L36 AND (AMYLO? OR ALZHEIM?)) NOT (L26 OR
                L31 OR L37)
                D STAT QUE NOS
                D IBIB ABS HITSTR 1-29
L39         169 SEA ABB=ON  PLU=ON  6(W)(OXO(2W)HEXANO? OR OXOHEXANO?)
L40           3 SEA ABB=ON  PLU=ON  L39 AND L25
L41           1 SEA ABB=ON  PLU=ON  L40 NOT (L26 OR L31 OR L37 OR L38)
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                D IBIB ABS HITSTR L41 1

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L42          60 SEA ABB=ON  PLU=ON  6(W)(OXO(2W) HEXANO? OR OXOHEXANO?)
L43          15 SEA ABB=ON  PLU=ON  L42 AND (SAP OR AMYLO?)
L44          10 DUP REMOV L43 (5 DUPLICATES REMOVED)
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L45          10 SEA ABB=ON  PLU=ON  L42 AND ALZHEIM?
L46           8 DUP REM L45 (2 DUPLICATES REMOVED)
L47           1 SEA ABB=ON  PLU=ON  L46 NOT L44
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                D IBIB ABS L47 1
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FILE HOME

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 19 SEP 2005 HIGHEST RN 863478-08-4
DICTIONARY FILE UPDATES: 19 SEP 2005 HIGHEST RN 863478-08-4

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

FILE HCAPLUS

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FILE COVERS 1907 - 21 Sep 2005 VOL 143 ISS 13
FILE LAST UPDATED: 20 Sep 2005 (20050920/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 14 September 2005 (20050914/ED)

FILE RELOADED: 19 October 2003.

FILE MEDLINE
FILE LAST UPDATED: 20 SEP 2005 (20050920/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 15 Sep 2005 (20050915/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 15:44:19 ON 21 SEP 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 21 Sep 2005  VOL 143 ISS 13
FILE LAST UPDATED: 20 Sep 2005  (20050920/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L18              STR
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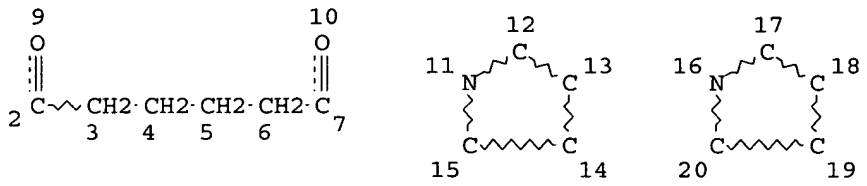


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  18

STEREO ATTRIBUTES: NONE
L20          538 SEA FILE=REGISTRY SSS FUL L18
L24          305 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L20
L25        12939 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SERUM(W)AMYLOID(W)(P OR
                 PROTEIN) OR SAP
L26            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 AND L25


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L26 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1080794 HCAPLUS
DOCUMENT NUMBER: 142:49214
TITLE: Compounds inhibiting the binding of **serum amyloid P** component (**SAP**) for treating osteoarthritis
INVENTOR(S): Pepys, Mark B.; Hawkins, Philip Nigel
PATENT ASSIGNEE(S): Pentraxin Therapeutics Limited, UK
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004108131	A1	20041216	WO 2004-GB2445	20040610

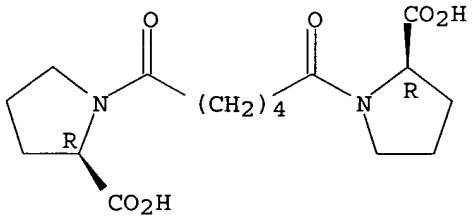
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-13386 A 20030610
OTHER SOURCE(S): MARPAT 142:49214

AB The invention discloses the use of an agent capable of inhibiting **serum amyloid P** component (**SAP**) ligand binding activity or depleting **SAP** from the plasma of a subject for the production of a medicament for treatment or prevention of osteoarthritis in the subject.

IT **224624-80-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compds. inhibiting binding of **serum amyloid P** component for treating osteoarthritis)
RN 224624-80-0 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:570143 HCAPLUS
DOCUMENT NUMBER: 141:119812
TITLE: Methods of detecting the inhibition of fibrocyte formation and methods and compositions for enhancing fibrocyte formation
INVENTOR(S): Gomer, Richard; Pilling, Darrell
PATENT ASSIGNEE(S): William Marsh Rice University, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004059318	A2	20040715	WO 2003-US41183	20031222
WO 2004059318	A3	20050506		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

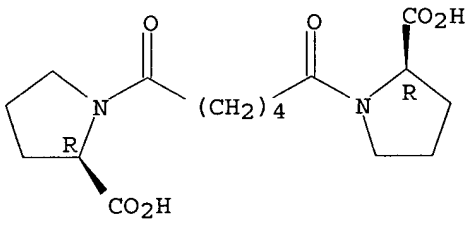
PRIORITY APPLN. INFO.:		
US 2002-436027P	P	20021223
US 2002-436046P	P	20021223
US 2003-515776P	P	20031030
US 2003-519467P	P	20031112
US 2003-525175P	P	20031126

AB The present invention relates to the ability of **SAP** to suppress the differentiation of monocytes into fibrocytes. It also relates to the ability of IL-4 and IL-3 to enhance the differentiation of monocytes into fibrocytes. Methods and compns. for binding **SAP**, decreasing **SAP** levels and suppressing **SAP** activity are provided. Methods of using, inter alia, CPHPC, the 4,6-pyruvate acetyl of beta-D-galactopyranose, ethanolamines, high EEO agarose, IL-4, and IL-13, and anti-**SAP** antibodies and fragments thereof to increase monocyte differentiation into fibrocytes are provided. These methods are useful in a variety of applications, including wound healing. Wound dressings are also provided. Finally, the invention includes assays for detecting the ability of various agents to modulate monocyte differentiation into fibrocytes and to detect monocyte defects.

IT **224624-80-0**, CPHPC
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(methods of detecting the inhibition of fibrocyte formation and methods and compns. for enhancing fibrocyte formation)

RN 224624-80-0 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L26 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:491182 HCAPLUS
DOCUMENT NUMBER: 139:53316
TITLE: Preparation of D-proline derivatives as prodrugs
INVENTOR(S): Huwyler, Joerg; Jakob-Roetne, Roland; Poli, Sonia Maria
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051836	A1	20030626	WO 2002-EP13827	20021206
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US 2003134891	A1	20030717	US 2002-307699	20021202
US 6903129	B2	20050607		
CA 2470037	AA	20030626	CA 2002-2470037	20021206
EP 1458680	A1	20040922	EP 2002-796578	20021206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002014932	A	20041130	BR 2002-14932	20021206
JP 2005515211	T2	20050526	JP 2003-552723	20021206
TW 225400	B1	20041221	TW 2002-91135829	20021211
PRIORITY APPLN. INFO.:			EP 2001-129793 A	20011214
			WO 2002-EP13827 W	20021206

OTHER SOURCE(S): MARPAT 139:53316
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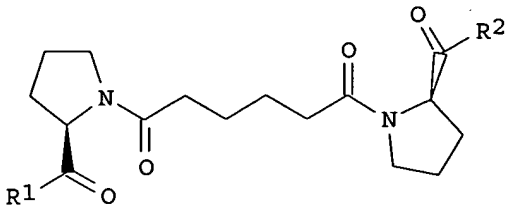


I

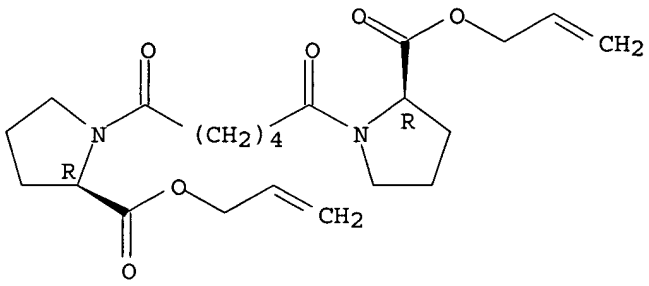
AB D-Proline derivs. I [R1, R2 independently are alkoxy, alkenyloxy, benzyloxy, OH, OCHMeO2C-alkyl, or OCH2CONR3R4 (with the proviso that only one of R1 or R2 may be OH); R3, R4 independently are H, alkyl, alkenyl, or cycloalkyl; or R1 and R2 together form the linking group X, where X is O(CH2)nCH:CH(CH2)nO or O(CH2)mO, where n is 1, 2 or 3 and m is 4-8] and their pharmaceutically-acceptable salts were prepared Compds. of the invention can be used for the treatment of diseases where **serum amyloid P** component depletion has a beneficial effect, in particular in the treatment or prevention of all forms of central and systemic amyloidosis. Thus, (R)-1-[6-((R)-2-carboxypyrrolidin-1-yl)-6-oxohexanoyl]pyrrolidine-2-carboxylic acid (I; R1 = R2 = OH) was treated with 2-chloroacetamide in DMF in the presence of NaI and Et3N to afford 44% I (R1 = R2 = CH2CONH2). Tests using rat and human liver microsome incubations showed that compds. of the invention are potential prodrugs for the parent diacid II.

IT **548487-31-6P 548487-32-7P 548487-33-8P 548487-34-9P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of D-proline derivs. as prodrugs)

RN 548487-31-6 HCAPLUS

CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, di-2-propenyl ester (9CI) (CA INDEX NAME)

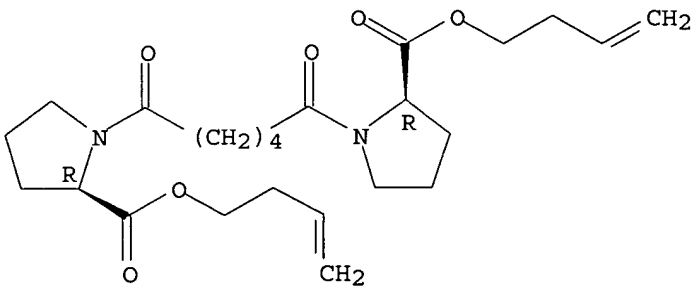
Absolute stereochemistry.



RN 548487-32-7 HCAPLUS

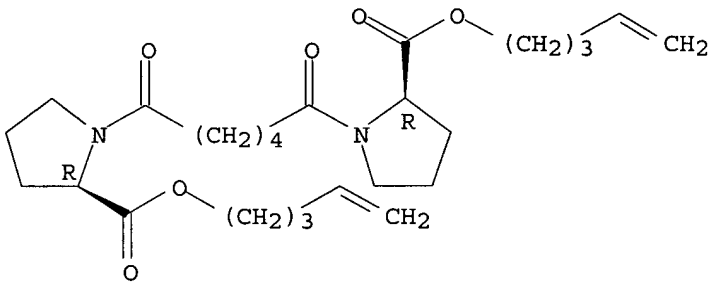
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, di-3-butenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



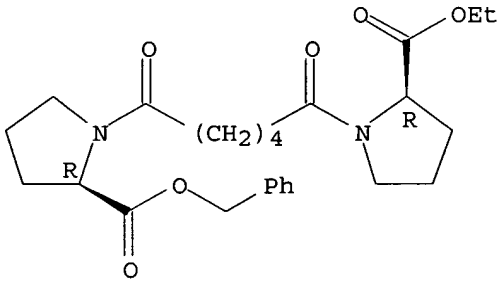
RN 548487-33-8 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, di-4-pentenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 548487-34-9 HCAPLUS
CN D-Proline, 1-[1,6-dioxo-6-[2-[(phenylmethoxy)carbonyl]-1-pyrrolidinyl]hexyl]-, ethyl ester (9CI) (CA INDEX NAME)

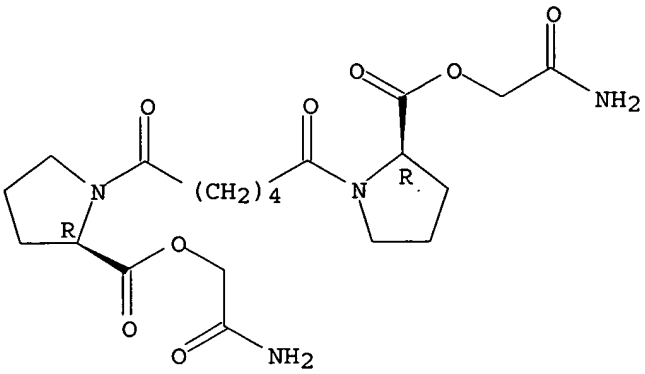
Absolute stereochemistry.



IT **548487-18-9P 548487-19-0P 548487-20-3P**
548487-21-4P 548487-22-5P 548487-23-6P
548487-24-7P 548487-25-8P 548487-26-9P
548487-27-0P 548487-28-1P 548487-29-2P
548487-30-5P 548487-35-0P 548487-36-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of D-proline derivs. as prodrugs)
RN 548487-18-9 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis(2-amino-2-oxoethyl)

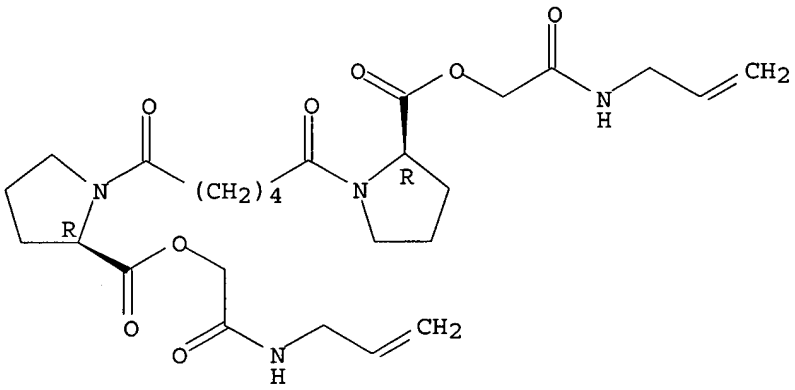
ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



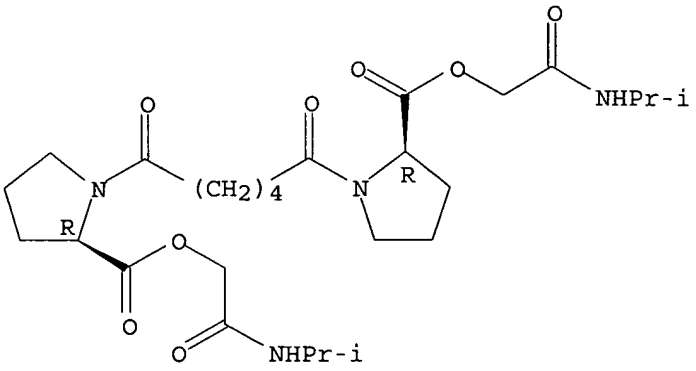
RN 548487-19-0 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[2-oxo-2-(2-propenylamino)ethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



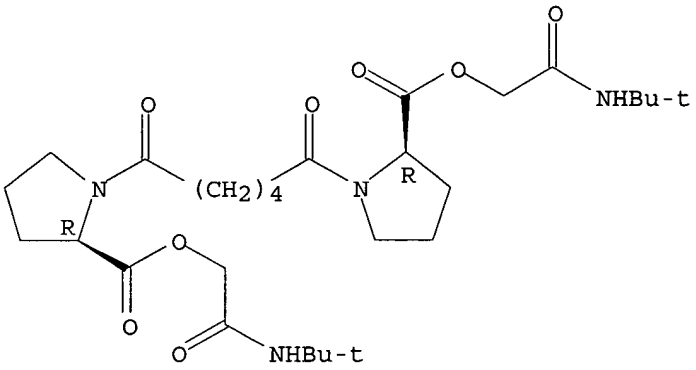
RN 548487-20-3 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[2-[(1-methylethyl)amino]-2-oxoethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



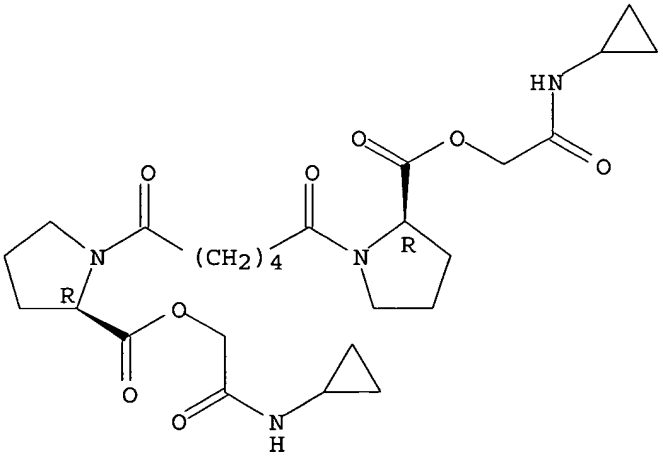
RN 548487-21-4 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[2-[(1,1-dimethylethyl)amino]-2-oxoethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



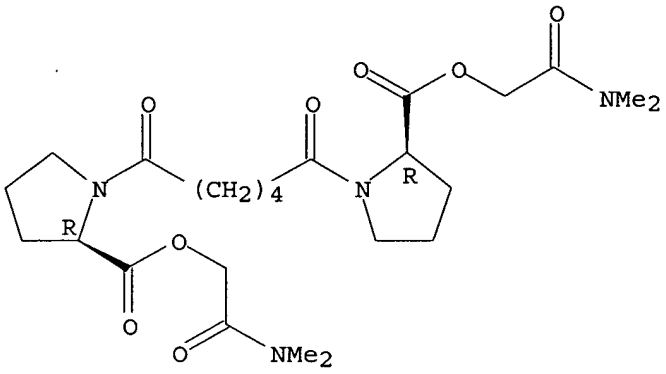
RN 548487-22-5 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[2-(cyclopropylamino)-2-oxoethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



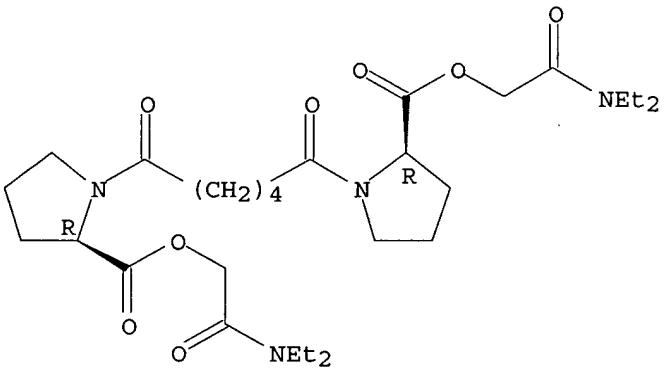
RN 548487-23-6 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[2-(dimethylamino)-2-oxoethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



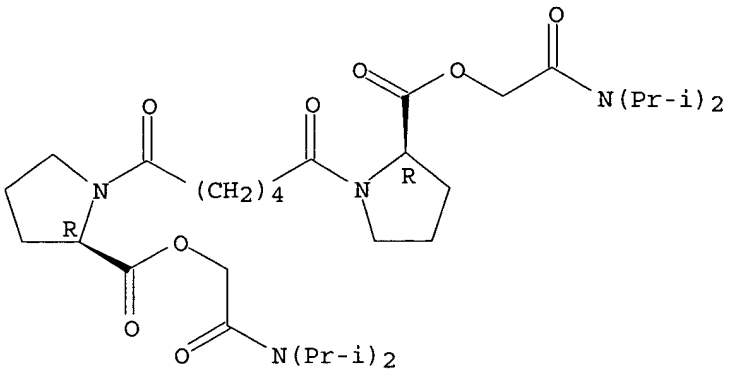
RN 548487-24-7 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[2-(diethylamino)-2-oxoethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



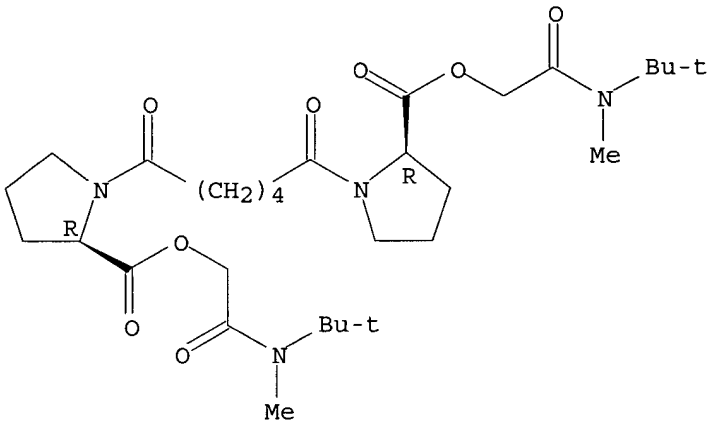
RN 548487-25-8 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[2-[bis(1-methylethyl)amino]-2-oxoethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



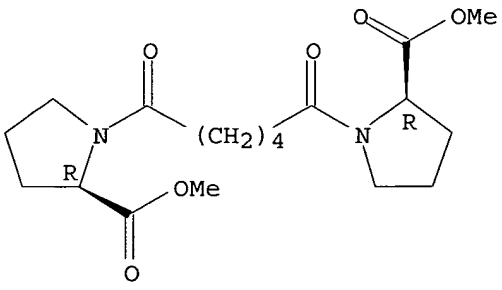
RN 548487-26-9 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[2-[(1,1-dimethylethyl)methylamino]-2-oxoethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 548487-27-0 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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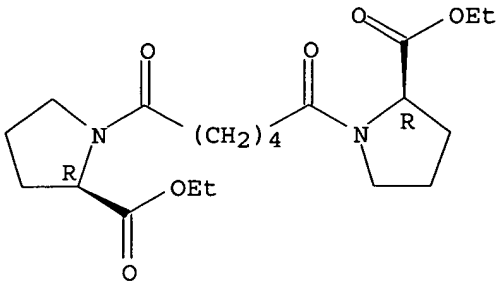
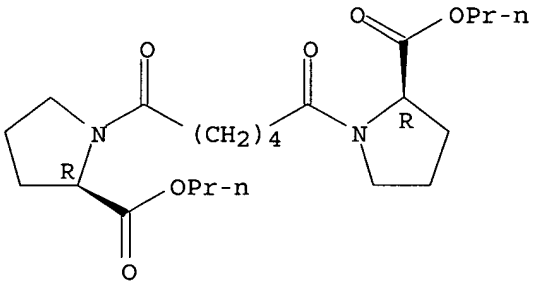
Absolute stereochemistry.



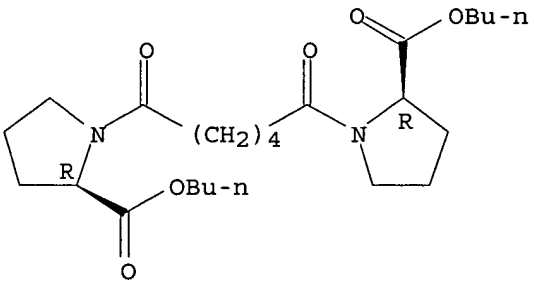
RN 548487-29-2 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, dipropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



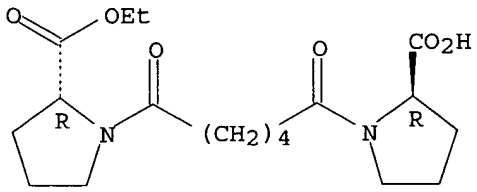
RN 548487-30-5 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, dibutyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



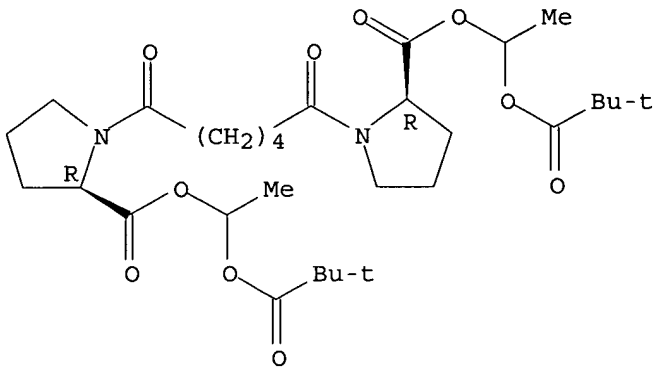
RN 548487-35-0 HCAPLUS
CN D-Proline, 1-[6-[(2R)-2-carboxy-1-pyrrolidinyl]-1,6-dioxohexyl]-, 2-ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



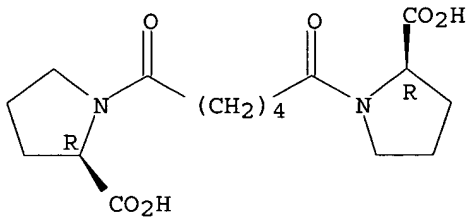
RN 548487-36-1 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis-, bis[1-(2,2-dimethyl-1-oxopropoxy)ethyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **224624-80-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of D-proline derivs. as prodrugs)
RN 224624-80-0 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

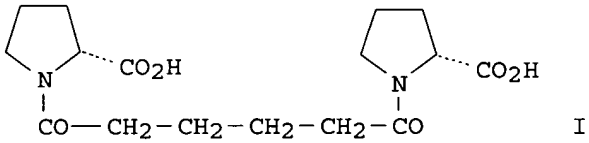
L26 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:133025 HCAPLUS
DOCUMENT NUMBER: 138:163606
TITLE: Pyrrolidine derivatives for depletion of an unwanted protein population from plasma
INVENTOR(S): Pepys, Mark B.
PATENT ASSIGNEE(S): University College London, UK
SOURCE: PCT Int. Appl., 54 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013508	A1	20030220	WO 2002-GB3504	20020729
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1418905	A1	20040519	EP 2002-751356	20020729
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005501071	T2	20050113	JP 2003-518517	20020729

PRIORITY APPLN. INFO.:
GB 2001-19370 A 20010808
US 2001-985699 A 20011105
WO 2002-GB3504 W 20020729

OTHER SOURCE(S): MARPAT 138:163606
GI



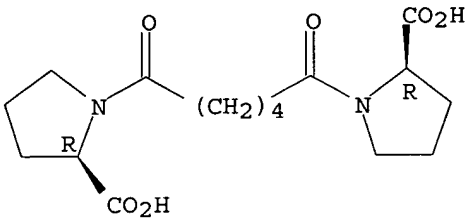
I

AB An agent for the depletion of an unwanted protein population from the plasma of a subject comprises a plurality of ligands covalently co-linked so as to form a complex with a plurality of proteins present, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins, wherein the agent is a non-proteinaceous agent other than a D-proline derivative E.g., I specifically targets **SAP** in vivo, through the specific ligand binding capacity of **SAP**, but addnly., as a consequence of the drug's palindromic structure, it causes aggregation of native pentameric **SAP** mols. into decameric drug **SAP** complexes that are then promptly cleared by the liver.

IT **224624-80-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrrolidine derivs. for depletion of an unwanted protein population from plasma)

RN 224624-80-0 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

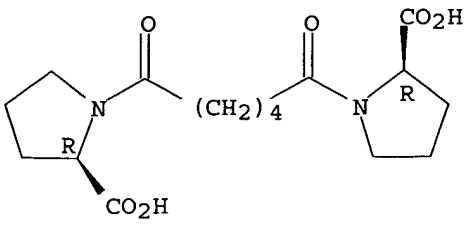
Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:362347 HCAPLUS
DOCUMENT NUMBER: 137:320267
TITLE: Targeted pharmacological depletion of **serum amyloid P** component for treatment of human amyloidosis
AUTHOR(S): Pepys, M. B.; Herbert, J.; Hutchinson, W. L.; Tennent, G. A.; Lachmann, H. J.; Gallimore, J. R.; Lovat, L. B.; Bartfai, T.; Alanine, A.; Hertel, C.; Hoffmann, T.; Jakob-Roetne, R.; Norcross, R. D.; Kemp, J. A.; Yamamura, K.; Suzuki, M.; Taylor, G. W.; Murray, S.; Thompson, D.; Purvis, A.; Kolstoe, S.; Wood, S. P.; Hawkins, P. N.
CORPORATE SOURCE: Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine, Royal Free and University College Medical School, London, NW3 2PF, UK
SOURCE: Nature (London, United Kingdom) (2002), 417(6886), 254-259
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The normal plasma protein **serum amyloid P** component (**SAP**) binds to fibrils in all types of amyloid deposits, and contributes to the pathogenesis of amyloidosis. In order to intervene in this process we have developed a drug, R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid, that is a competitive inhibitor of **SAP** binding to amyloid fibrils. This palindromic compound also crosslinks and dimerizes **SAP** mols., leading to their very rapid clearance by the liver, and thus produces a marked depletion of circulating human **SAP.** This mechanism of drug action potently removes **SAP** from human amyloid deposits in the tissues and may provide a new therapeutic approach to both systemic amyloidosis and diseases associated with local amyloid, including Alzheimer's disease and type 2 diabetes.
IT **224624-80-0**, Ro 63-8695
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CPHPC; targeted pharmacol. depletion of **serum amyloid P** component for treatment of human amyloidosis)
RN 224624-80-0 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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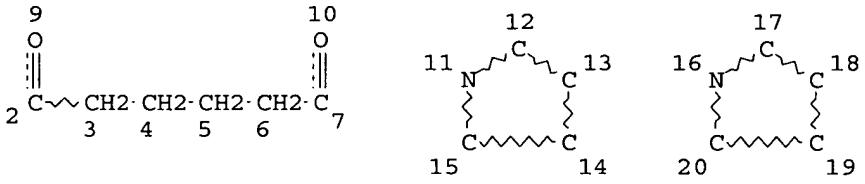
L18 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
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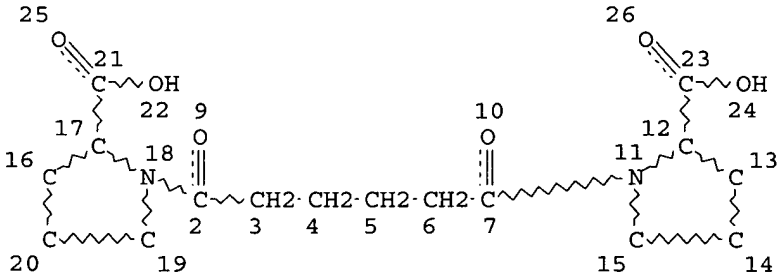
L24 305 SEA FILE=HCAPLUS ABB=ON PLU=ON L20
L25 12939 SEA FILE=HCAPLUS ABB=ON PLU=ON SERUM(W)AMYLOID(W)(P OR PROTEIN) OR SAP
L26 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND L25
L27 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

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STEREO ATTRIBUTES: NONE
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L30           9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29
L31           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L30 NOT L26


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=>

=> d ibib abs hitstr l31 1-4

L31  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:42246  HCAPLUS
DOCUMENT NUMBER:          138:107006
TITLE:                    Preparation of amino acid derivatives as prolyl
                          oligopeptidase inhibitors
INVENTOR(S):              Gynther, Jukka; Maennistoe, Pekka; Wallen, Erik;
                          Christiaans, Johannes; Forsberg, Markus; Poso, Antti;
                          Venaelaeinen, Jarkko; Helkala, Elina
PATENT ASSIGNEE(S):       Orion Corporation, Finland
SOURCE:                   PCT Int. Appl., 78 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2003004468         A1    20030116    WO 2002-FI607           20020704
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
             NE, SN, TD, TG
     CA 2450857            AA    20030116    CA 2002-2450857         20020704
     EP 1401810            A1    20040331    EP 2002-745453          20020704
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
     JP 2004535459         T2    20041125    JP 2003-510636          20020704
     US 2005020677         A1    20050127    US 2004-482700          20040608
PRIORITY APPLN. INFO.:                       FI 2001-1466         A  20010704
                                             WO 2002-FI607        W  20020704

OTHER SOURCE(S):          MARPAT 138:107006
AB   Amino acid derivs. G-CO-Q-CO-aa-A [aa is a residue of an α-amino
     acid; Q is a covalent bond, (un)substituted (cyclo)alk(en)ylene, or
     arylene; A is (un)substituted alk(en)yl, carbo- or heterocyclyl; G = aa'-E
     (aa' is an α-amino acid residue and E is a group defined similarly
     to A) or an amino functionality containing a heterocyclic ring] or their
     pharmaceutically-acceptable salts were prepared for use as prolyl
     oligopeptide inhibitors, e.g., for the treatment of Alzheimer's disease.
     Thus, glutaric acid bis(L-prolylpyrrolidine) amide was prepared via coupling
```

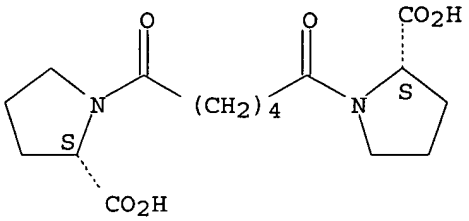
reactions and showed IC50 = 48 nM for inhibition of pig prolyl oligopeptidase.

IT **155885-27-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of amino acid derivs. as prolyl oligopeptidase inhibitors)

RN 155885-27-1 HCAPLUS

CN L-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:650987 HCAPLUS

DOCUMENT NUMBER: 137:325613

TITLE: Dicarboxylic Acid bis(L-Prolyl-pyrrolidine) Amides as Prolyl Oligopeptidase Inhibitors

AUTHOR(S): Wallen, Erik A. A.; Christiaans, Johannes A. M.; Forsberg, Markus M.; Venaelaeinen, Jarkko I.; Maennistoe, Pekka T.; Gynther, Jukka

CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kuopio, Kuopio, FIN-70211, Finland

SOURCE: Journal of Medicinal Chemistry (2002), 45(20), 4581-4584
CODEN: JMCMAR; ISSN: 0022-2623

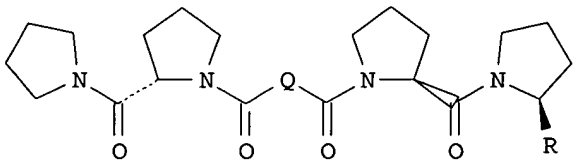
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:325613

GI



I

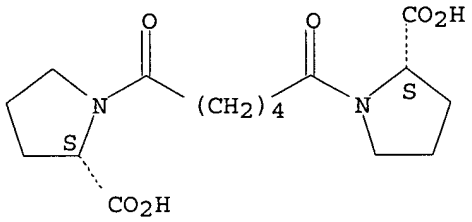
AB New dicarboxylic acid bis(L-prolyl-pyrrolidine) amides I [Q = (CH2)n, n = 2-4 with R = H; Q = CH2C(Me)2CH2, R = H; Q = o-, m-, p-phenylene with R = H; Q = m-phenylene with R = CHO, CN, COCH2OH] were synthesized, and their inhibitory activity against prolyl oligopeptidase from pig brain was tested in vitro. As compared with prolyl oligopeptidase inhibitors described earlier, I has in common an L-prolyl-pyrrolidine moiety, but the typical lipophilic acyl end group is replaced by another

L-prolyl-pyrrolidine moiety connected sym. with a short dicarboxylic acid linker. I is a new type of peptidomimetic prolyl oligopeptidase inhibitor.

IT **155885-27-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of dicarboxylic acid bis(prolyl-pyrrolidine)amides as inhibitors of prolyl oligopeptidase)

RN 155885-27-1 HCAPLUS
CN L-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:343650 HCAPLUS
DOCUMENT NUMBER: 130:352548
TITLE: Synthesis of D-proline derivatives for treatment of amyloidosis
INVENTOR(S): Hertel, Cornelia; Hoffmann, Torsten; Jakob-Roetne, Roland; Norcross, Roger David
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: Eur. Pat. Appl., 77 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 915088	A1	19990512	EP 1998-119986	19981022
EP 915088	B1	20020918		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 224366	E	20021015	AT 1998-119986	19981022
PT 915088	T	20030131	PT 1998-119986	19981022
ES 2182203	T3	20030301	ES 1998-119986	19981022
US 6103910	A	20000815	US 1998-179652	19981027
CA 2252163	AA	19990430	CA 1998-2252163	19981028
NZ 332530	A	20000526	NZ 1998-332530	19981028
IL 126787	A1	20031210	IL 1998-126787	19981028
ZA 9809889	A	19990430	ZA 1998-9889	19981029
AU 9889599	A1	19990520	AU 1998-89599	19981029
AU 750734	B2	20020725		
JP 11209343	A2	19990803	JP 1998-307719	19981029
JP 3048558	B2	20000605		
TW 585854	B	20040501	TW 1998-87117984	19981029

NO 9805059	A	19990503	NO 1998-5059	19981030
NO 312064	B1	20020311		
CN 1217327	A	19990526	CN 1998-123674	19981030
BR 9804378	A	20000613	BR 1998-4378	19981030
SG 74094	A1	20000718	SG 1998-4381	19981030
RU 2201937	C2	20030410	RU 1998-120057	19981030
HR 980572	B1	20040630	HR 1998-980572	19981030
US 6262089	B1	20010717	US 2000-505375	20000216
US 6512001	B1	20030128	US 2000-636076	20000810
US 2003100770	A1	20030529	US 2002-186781	20020701
US 6740760	B2	20040525		

PRIORITY APPLN. INFO.:

EP 1997-119031	A	19971031
EP 1998-113851	A	19980724
US 1998-179652	A3	19981027
US 2000-505375	A3	20000216
US 2000-636076	A3	20000810

OTHER SOURCE(S): MARPAT 130:352548

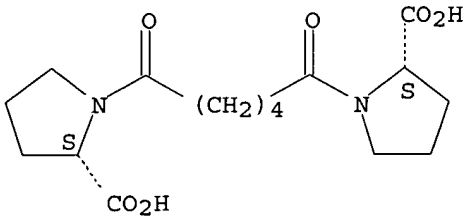
AB D-Proline derivs. R-X-CO-D-Pro-OH [R = SH, benzyl, Ph, hydroxy- or alkoxy-Ph, or D-Pro-OH; X = (CH2)n, (CH2)nCHR2, (CH2)nOCH2, NHCH2, benzyl, CH:CR2, CH(OH)CH2, thiazol-2,5-diyl (n = 0-3, R2 = alkyl, alkoxy, benzyl)] and related di-D-proline derivs. linked at X by SS, (CH2)n, O, NH, NR2, phenylene, etc., as well as corresponding 4-halo and 3,4-didehydro derivs., were prepared for the treatment of amyloidosis. Thus, (R)-1-[(S)-3-[(S)-3-[(R)-2-carboxypyrrolidin-1-yl]-2-methyl-3-oxopropyl-dithio]-2-methyl-propionyl]pyrrolidine-2-carboxylic acid was prepared by acylation of D-proline tert-Bu ester with AcSCH2CHMeCOCl, followed by ester cleavage and disulfide coupling.

IT **155885-27-1P 224624-80-0P 224625-89-2P**
224625-92-7P 224625-94-9P 224626-00-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of D-proline derivs. for treatment of amyloidosis)

RN 155885-27-1 HCAPLUS

CN L-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

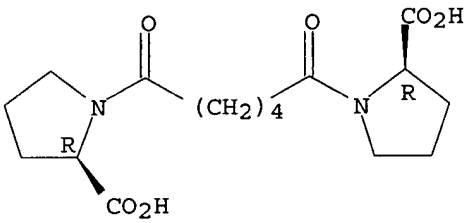
Absolute stereochemistry.



RN 224624-80-0 HCAPLUS

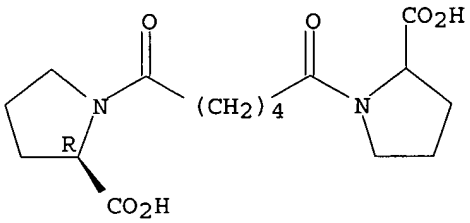
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

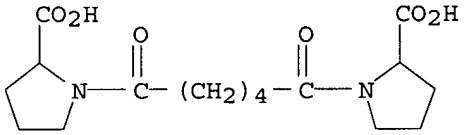


RN 224625-89-2 HCAPLUS
CN Proline, 1-[6-[(2R)-2-carboxy-1-pyrrolidinyl]-1,6-dioxohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

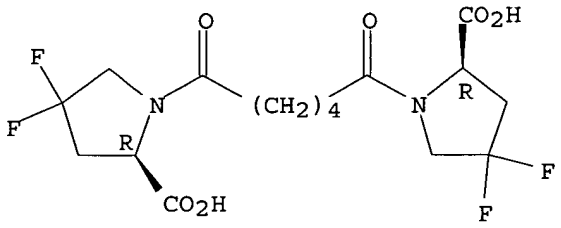


RN 224625-92-7 HCAPLUS
CN Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)



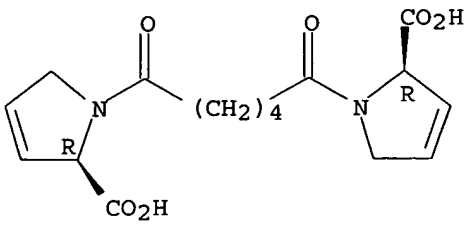
RN 224625-94-9 HCAPLUS
CN D-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis[4,4-difluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 224626-00-0 HCAPLUS
CN 1H-Pyrrole-2-carboxylic acid, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis[2,5-dihydro-, (2R,2'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



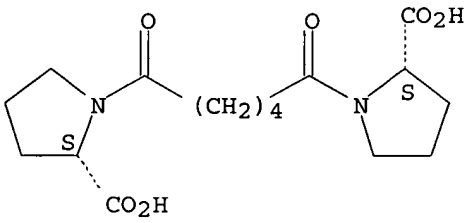
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:497803 HCAPLUS
DOCUMENT NUMBER: 121:97803
TITLE: Electrolytic capacitor solution containing amide-containing dicarboxylic acid
INVENTOR(S): Ue, Makoto; Takeda, Masayuki; Sato, Tomohiro
PATENT ASSIGNEE(S): Mitsubishi Petrochemical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

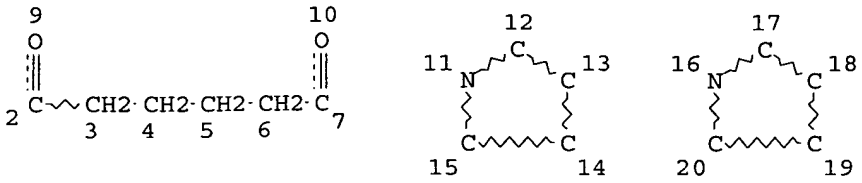
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06061099	A2	19940304	JP 1992-208759	19920805
PRIORITY APPLN. INFO.:			JP 1992-208759	19920805

OTHER SOURCE(S): MARPAT 121:97803
GI For diagram(s), see printed CA Issue.
AB The solution contains amide-containing dicarboxylic acids or their salts. The dicarboxylic acids may be (HO2CYNRCO)2X or I (X = dicarboxylic acid residue; Y = amino acid residue; Z = alkyl, H; Z = heterocyclic amino acid residue). The solution showed good low-temperature property.
IT **155885-27-1**
RL: DEV (Device component use); USES (Uses)
(electrolytic capacitor solution containing, with good low-temperature property)
RN 155885-27-1 HCAPLUS
CN L-Proline, 1,1'-(1,6-dioxo-1,6-hexanediyl)bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> => d stat que
L18 STR

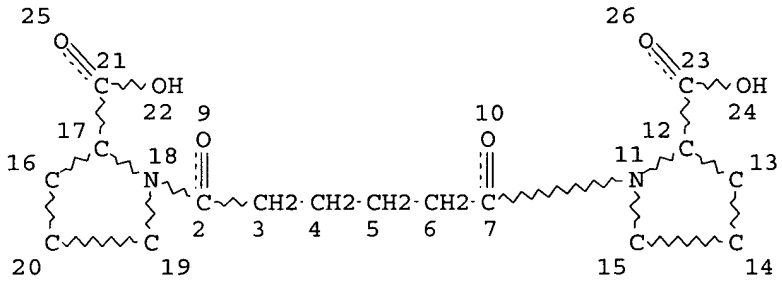


NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE

L20 538 SEA FILE=REGISTRY SSS FUL L18
L24 305 SEA FILE=HCAPLUS ABB=ON PLU=ON L20
L25 12939 SEA FILE=HCAPLUS ABB=ON PLU=ON SERUM(W)AMYLOID(W)(P OR PROTEIN) OR SAP
L26 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND L25
L27 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE

L28 6 SEA FILE=REGISTRY SUB=L20 SSS FUL L27
L29 SEL PLU=ON L28 1- CHEM : 8 TERMS
L30 9 SEA FILE=HCAPLUS ABB=ON PLU=ON L29
L31 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 NOT L26
L35 1 SEA FILE=REGISTRY ABB=ON PLU=ON D-PROLINE/CN
L36 1543 SEA FILE=HCAPLUS ABB=ON PLU=ON L35 OR D(W)PROLINE
L37 3 SEA FILE=HCAPLUS ABB=ON PLU=ON (L36 AND L25) NOT (L26 OR L31)

=>
=>

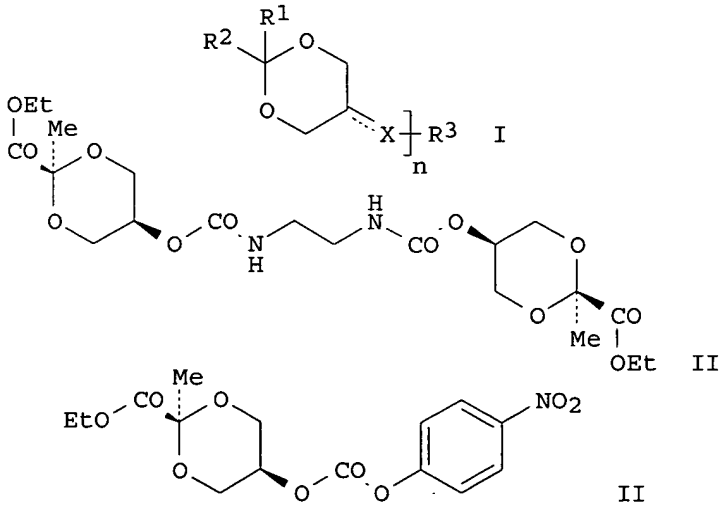
=> d ibib abs hitstr l37 1-3

L37 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:996151 HCAPLUS
DOCUMENT NUMBER: 141:424379
TITLE: Preparation of glycerol cyclic pyruvates as multivalent inhibitors of **serum amyloid P** component (**SAP**)
INVENTOR(S): Bundle, David; Kitov, Pavel; Ng, Kenneth Kai-Sing; Ho, Jason Gay Shuen
PATENT ASSIGNEE(S): Theracarb Inc., Can.
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004099173	A1	20041118	WO 2004-CA712	20040512

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-469633P P 20030512
OTHER SOURCE(S): MARPAT 141:424379
GI



AB Glycerol cyclic pyruvate derivs., such as I [R1 = carboxy, carboximido, tetrazolyl; R2 = alkyl; R3 = H, oligosaccharide, saccharide, peptide,

oliogocarbamate, etc.; X = linking group, such as O, S, NH, OC(O), or OC(O)N with an arylene, alkylene, peptide, saccharide, heterocyclic, etc.], were prepared for therapeutic use in the treatment or prevention of amyloidosis and diseases associated with amyloidosis, such as Alzheimer's disease and maturity onset diabetes mellitus. Thus, cyclic glycerol derivative II was prepared in 84% yield by a reaction of H2N(CH2)2NH2 with carbonate ester III using Et2N in CH2Cl2. The prepared cyclic glycerol derivs. were assayed for inhibition of binding of immobilized N-(10-undecenoyl)-**D-proline** to **SAP.**

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:931218 HCAPLUS
DOCUMENT NUMBER: 140:788
TITLE: C-reactive protein-binding ligands for the treatment and prevention of tissue damage
INVENTOR(S): Pepys, Mark B.; Ley, Steven Victor; Cobb, Alexander John Andre
PATENT ASSIGNEE(S): University College London, UK
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003097104	A1	20031127	WO 2003-GB2096	20030514
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2485852	AA	20031127	CA 2003-2485852	20030514
EP 1503800	A1	20050209	EP 2003-727670	20030514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: GB 2002-11136 A 20020515
WO 2003-GB2096 W 20030514

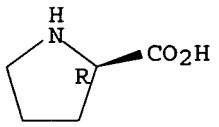
OTHER SOURCE(S): MARPAT 140:788

AB The invention discloses an agent for use in medicine, comprising a plurality of ligands covalently co-linked so as to form a complex with a plurality of C-reactive protein (CRP) mols. in the presence thereof, wherein (i) at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on the CRP mols.; or (ii) at least one of the ligands is capable of being bound by a ligand binding site present on a CRP mol., and at least one other of the ligands is capable of being bound by a ligand binding site present on a **serum amyloid P** component (**SAP**) mol.
Preparation and inhibitory activity of 1,6-bis[(((trimethylammonium)ethoxy)phosphinyl)oxy]hexane (phosphocholine-hexane-phosphocholine) is described.

IT **344-25-2D, D-Proline**, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(C-reactive protein-binding ligands for the treatment and prevention of tissue damage)
RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

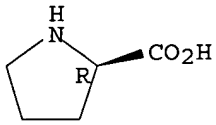
Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:233001 HCAPLUS
DOCUMENT NUMBER: 112:233001
TITLE: Effects of amino acid isomers on canine renal hemodynamics
AUTHOR(S): Premen, Andre J.; Dobbins, David E.
CORPORATE SOURCE: Dep. Physiol., Uniformed Serv. Univ. Health Sci., Bethesda, MD, 20814-4799, USA
SOURCE: American Journal of Physiology (1990), 258(4, Pt. 2), F799-F804
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It was determined whether the renal hemodynamic response to amino acid infusion in dogs is stereospecific. The renal hemodynamic effects of 2 isomers (L and D) of an amino acid mixture of serine, alanine, and proline (**SAP** ; 0.051 mmol/kg/min) were examined in anesthetized dogs. The i.v. infusion of L-**SAP** significantly elevated the renal blood flow (RBF) and glomerular filtration rate (GFR) by 33% and 30%, resp., over 1 h. DL-**SAP** elevated RBF and GFR by only 14% and 13%, resp. Yet D-**SAP** failed to elevate either RBF or GFR over 1 h. The i.v. mannitol (940 milliosmoles/kg; osmotic control) also failed to elevate renal hemodynamics. In other dogs, intrarenal infusion of L-, but not D-, **SAP** marginally elevated RBF and GFR by 13% and 12%, resp., over 1 h. Infusion of α-aminoisobutyric acid (0.051 mmol/kg/min), an amino acid analog that is cotransported with Na+ but not metabolized by renal cells, elevated RBF and GFR by 22% and 18%, resp., over 1 h. Evidently, vascular infusion of L, but not D, isomers of amino acids elevate RBF and GFR. Amino acid stereospecificity seems to be important in the renal vascular response to amino acid infusion in dogs.
IT **344-25-2, D-Proline**
RL: BIOL (Biological study)
(kidney hemodynamics response to, stereospecificity in relation to)
RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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=> => d stat que nos
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L20         538 SEA FILE=REGISTRY SSS FUL L18
L24         305 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L20
L25       12939 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SERUM(W)AMYLOID(W)(P OR
                PROTEIN) OR SAP
L26           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 AND L25
L27             STR
L28           6 SEA FILE=REGISTRY SUB=L20 SSS FUL L27
L29             SEL  PLU=ON  L28 1- CHEM :        8 TERMS
L30           9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29
L31           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L30 NOT L26
L35           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  D-PROLINE/CN
L36        1543 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L35 OR D(W)PROLINE
L37           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L36 AND L25) NOT (L26 OR
                L31)
L38          29 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L36 AND (AMYLO? OR ALZHEIM?))
                 NOT (L26 OR L31 OR L37)


=> d ibib abs hitstr 1-29

L38  ANSWER 1 OF 29  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:729611  HCAPLUS
DOCUMENT NUMBER:          143:206465
TITLE:                    Therapeutic and carrier molecules
INVENTOR(S):              Ferrante, Antonio; Rathjen, Deborah Ann
PATENT ASSIGNEE(S):       Peplin Biolipids Pty Ltd, Australia
SOURCE:                   PCT Int. Appl., 180 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2005073164         A1    20050811    WO 2005-AU98            20050128
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2004-540604P     P  20040130
```

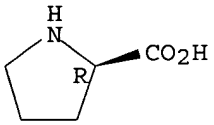
AB The present invention relates generally to compds. comprising a hydrocarbon chain portion and more particular to compds. comprising chemical derivatizations of the hydrocarbon chain which are useful therapeutic and prophylactic mols. The present invention further provides compds. where the hydrocarbon chain portion is a carrier mol. for functional groups, moieties or agents. The present invention can include naturally including polyunsatd. fatty acids as well as synthetic, modified or derivatized polyunsatd. fatty acids. Furthermore. these polyunsatd. fatty acids can be conjugated to amino acids, peptides or proteins. The compds. of the present invention are particularly useful in the treatment and prophylaxis of a range of conditions including cancers, protein kinase c(PKC)- or NFκB-related- or -associated conditions, cardiovascular conditions, pain, inflammatory conditions, vascular or immunol. conditions such as diabetes, neurol. conditions and infection by a range of viruses or prokaryotic or eukaryotic organisms. The present invention further provides pharmaceutical compns. and methods of medical treatment.

IT **344-25-2D, D-Proline**, conjugates
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrocarbon chains as therapeutic and carrier mols. for amino acids and proteins for treatment of disease)

RN 344-25-2 HCAPLUS

CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:673292 HCAPLUS
DOCUMENT NUMBER: 143:172866
TITLE: Preparation of isothiazole dioxides as CXC- and CC-chemokine receptor ligands
INVENTOR(S): Taveras, Arthur G.; Zheng, Junying; Biju, Purakkattle J.; Yu, Younong; Chao, Jianhua; Fine, Jay; Lundell, Daniel; Priestley, Tony; Reggiani, Angelo; Merritt, J. Robert; Baldwin, John J.; Lai, Gaifa; Wu, Minglang
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia Drug Discovery, Inc.
SOURCE: PCT Int. Appl., 427 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005068460	A1	20050728	WO 2004-US42720	20041220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,				

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-531693P P 20031222

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

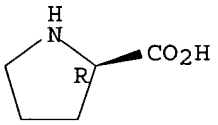
AB Disclosed are novel compds. I [D, E = N, CR50; provided that D and E are not the same (one is N and the other is CR50); R50 = H, CF3, CN, etc.; A = (hetero)aryl, (hetero)arylalkyl; B = (hetero)aryl] and the pharmaceutically acceptable salts and solvates thereof. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and cardiac reperfusion injury, pain (e.g., acute pain, acute and chronic inflammatory pain, and neuropathic pain) using a compound I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 68% yield from the isothiazoledioxide III and the amine IV.pTSA (preparation of reactants given). Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7 are given.

IT **344-25-2, D-Proline**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of isothiazole dioxides as CXC- and CC-chemokine receptor ligands)

RN 344-25-2 HCAPLUS

CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:638859 HCAPLUS

DOCUMENT NUMBER: 143:153384

TITLE: Preparation of diaminothiadiazoles as CXC- and CC-chemokine receptor ligands

INVENTOR(S): Biju, Purakkattle J.; Taveras, Arthur G.; Yu, Younong; Zheng, Junying; Chao, Jianhua; Aki, Cynthia J.; Fine, Jay; Lundell, Daniel; Priestley, Tony; Reggiani, Angelo; Merritt, J. Robert; Baldwin, John J.

PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia Drug Discovery, Inc.

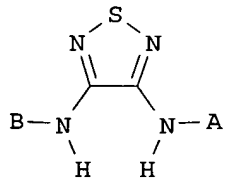
SOURCE: PCT Int. Appl., 593 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005066147	A1	20050721	WO 2004-US42060	20041216

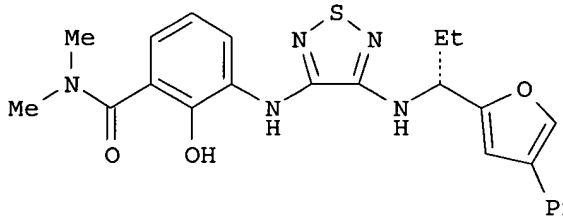
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-531311P P 20031219
US 2003-531713P P 20031222

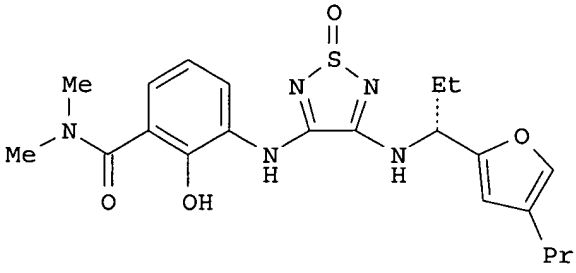
GI



I



II



III

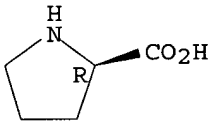
AB Disclosed are diaminothiadiazoles I [A = (hetero)aryl, (hetero)arylmethyl (substituted at CH2), etc.; B = (hetero)aryl] and the pharmaceutically acceptable salts and solvates thereof. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis,

angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and ischemia reperfusion injury, acute pain, acute and chronic inflammatory pain, and neuropathic pain using I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 43% yield from its monooxide III (preparation given). Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7 are given.

IT **344-25-2, D-Proline**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of diaminothiadiazoles as CXC- and CC-chemokine receptor ligands)

RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

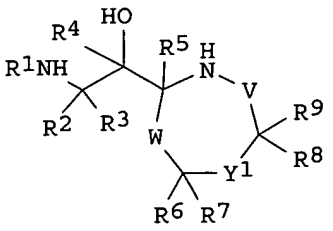


REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:141026 HCAPLUS
DOCUMENT NUMBER: 142:240330
TITLE: Preparation of cyclic amine BACE-1 inhibitors having a heterocyclic substituent
INVENTOR(S): Cumming, Jared N.; Huang, Ying; Li, Guoqing; Iserloh, Ulrich; Stamford, Andrew; Strickland, Corey; Voigt, Johannes H.; Wu, Yusheng; Pan, Jianping; Guo, Tao; Hobbs, Douglas W.; Le, Thuy X. H.; Lowrie, Jeffrey F.
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia Drug Discovery, Inc.
SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005014540	A1	20050217	WO 2004-US25748	20040804
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005043290	A1	20050224	US 2004-911030	20040804

PRIORITY APPLN. INFO.: US 2003-493646P P 20030808
OTHER SOURCE(S): MARPAT 142:240330
GI



I

AB Disclosed are novel compds., e.g., I [R1 = azcycloalkylcarbamoyl, carbamoyl (from piperazine, piperidine or pyrrolidine derivs.); X = O, C(R14)2, N(R); Z is -C(R14)2- or -N(R)-; t is 0, 1, 2 or 3; R, R2 = H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, alkenyl or alkynyl; R3, R4 = H, alkyl; R5 = H, alkyl, cycloalkyl, aryl, heteroaryl; R14 = H, alkyl, alkenyl, alkynyl, halo, -CN, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, -OR35, N(R24)(R25)or SR35; R41 is alkyl, cycloalkyl, -S02(alkyl), -C(O)-alkyl, -C(O)-cycloalkyl or -alkyl-NH-C(O)CH3; W = (CR10R11)l; V = (CR12R13)n; Y1 = (Y)m; Y = CR30R31; l = 0 - 3; m = 0, 1; n = 0 - 3 (whereby the sum of l + n = 0 - 3); etc.] or a pharmaceutically acceptable salt or solvate thereof. Also disclosed are pharmaceutical compns. comprising the compds. I and methods of treating cognitive or neurodegenerative diseases with compds. I (no data). Also disclosed are pharmaceutical compns. and methods of treatment comprising compds. I in combination with other agents useful in treating cognitive or neurodegenerative diseases (no data).
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:698210 HCAPLUS
DOCUMENT NUMBER: 141:238805
TITLE: Identification and characterization of proline racemase from Trypanosoma cruzi, definition of the protein signatures, and assays for detecting D-amino acid and for screening proline racemase inhibitors
INVENTOR(S): Minoprio, Paola; Chamond, Nathalie; Degrave, Wim; Berneman, Armand
PATENT ASSIGNEE(S): Institut Pasteur, Fr.
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

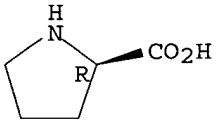
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004072223 A2 20040826 WO 2004-IB861 20040211
WO 2004072223 A3 20041007
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2003-446263P P 20030211

AB This invention relates to the identification and characterization of racemases and definition of protein signatures of these racemases. More particularly, this invention relates to the identification of nucleic acid mols. encoding a peptide consisting of a motif characteristic of the protein signatures, and to the peptides consisting of these motifs. This invention also relates to antibodies specific for the peptides and to immune complexes of these antibodies with the peptides. More specifically, the nucleotide sequences and the encoded amino acid sequences of proline racemase isoenzymes from Trypanosoma cruzi are disclosed. Cloning and recombinant expression of the T. cruzi proline racemase isoenzymes is described. Structural and kinetic properties of the T. cruzi proline racemase isoenzymes are characterized. Further, the invention relates to methods and kits for detecting racemases using the nucleic acid mols. of the invention, as well as the peptides consisting of the motifs and antibodies to these peptides. A diagnostic assay for detecting a D-amino acid using a D-amino acid oxidase is also described. An assay for screening proline racemase inhibitors is provided. Proline racemase protein signatures are studied and putative proline racemases are identified in sequence databases. The amino acid sequences of the T. cruzi proline racemase isoenzymes signature motifs are disclosed.

IT **344-25-2, D-Proline**
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(identification and characterization of proline racemase from Trypanosoma cruzi, definition of protein signatures, and assays for detecting D-amino acid and for screening proline racemase inhibitors)
RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

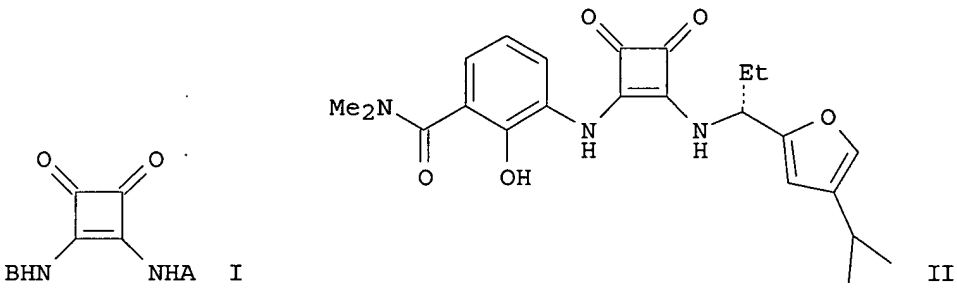


L38 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:609929 HCAPLUS
DOCUMENT NUMBER: 141:157023
TITLE: Preparation of 3,4-diaminocyclobutene-1,2-diones as CXC-chemokine receptor ligands
INVENTOR(S): Taveras, Arthur G.; Aki, Cynthia J.; Bond, Richard W.;

Chao, Jianping; Dwyer, Michael; Ferreira, Johan A.; Chao, Jianhua; Yu, Younong; Baldwin, John J.; Kaiser, Bernd; Li, Ge; Merritt, J. Robert; Biju, Purakkattle J.; Nelson, Kingsley H.; Rokosz, Laura L.; Jakway, James P.; Lai, Gaifa; Wu, Minglang; Hecker, Evan A.; Lundell, Daniel; Fine, Jay S.
PATENT ASSIGNEE(S): Schering Corporation and Pharmacopeia, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 352 pp., Cont.-in-part of U.S. Ser. No. 241,326.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

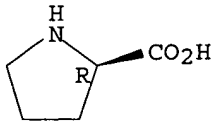
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004147559	A1	20040729	US 2003-630258	20030730
US 2004097547	A1	20040520	US 2002-208412	20020730
US 2004106794	A1	20040603	US 2002-241326	20020911
PRIORITY APPLN. INFO.:			US 2001-284026P	P 20010416
			US 2002-122841	B2 20020415
			US 2002-208412	A2 20020730
			US 2002-241326	A2 20020911

OTHER SOURCE(S): MARPAT 141:157023
GI



AB Title compds. [I; A = (substituted) pyridylmethyl, thiazolylmethyl, benzofurylmethyl, isoxazolylmethyl, pyrazinylmethyl, triazolylmethyl, phenylalkyl, etc.; B = (substituted) Ph, benzotriazolyl, benzimidazolyl, imidazolyl, pyrazolyl, hydroxypyridinyl, thienyl, pyrrolyl, isothiazolyl, etc.], were prepared Thus, title compound (II) (preparation outlined) showed Ki =
0.8 nM in a CXCR2 SPA receptor binding assay.
IT **344-25-2, D-Proline**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of diaminocyclobutenediones as CXC chemokine receptor ligands)
RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L38 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:451668 HCAPLUS
DOCUMENT NUMBER: 141:23213
TITLE: Preparation of 3,4-di-substituted cyclobutene-1,2-diones as CXC-chemokine receptor ligands
INVENTOR(S): Taveras, Arthur G.; Aki, Cynthia J.; Bond, Richard W.; Chao, Jianping; Dwyer, Michael; Ferreira, Johan A.; Chao, Jianhua; Yu, Younong; Baldwin, John J.; Kaiser, Bernd; Li, Ge; Merritt, J. Robert; Biju, Purakkattle J.; Nelson, Kingsley H.; Rokosz, Laura L.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 331 pp., Cont.-in-part of U.S. Ser. No. 208,412.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004106794	A1	20040603	US 2002-241326	20020911
US 2004097547	A1	20040520	US 2002-208412	20020730
CA 2496676	AA	20040205	CA 2003-2496676	20030730
WO 2004011418	A1	20040205	WO 2003-US23785	20030730
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004147559	A1	20040729	US 2003-630258	20030730
EP 1539678	A1	20050615	EP 2003-772075	20030730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003013109	A	20050621	BR 2003-13109	20030730

PRIORITY APPLN. INFO.:		
US 2001-284026P	P	20010416
US 2002-122841	A2	20020415
US 2002-208412	A2	20020730
US 2002-241326	A	20020911
WO 2003-US23785	W	20030730

OTHER SOURCE(S): MARPAT 141:23213
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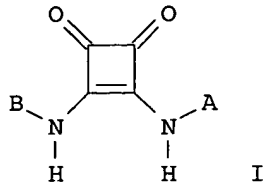

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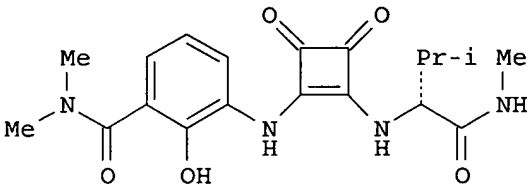


II

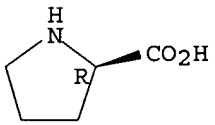
AB Title compds. I [A = (un)substituted heterocycle, heterocyclylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, etc.; B = (un)substituted aryl, heteroaryl, heterocycle, heteroarylarene, etc.], or a pharmaceutically acceptable salt or solvate thereof, are prepared and disclosed as cxc-chemokine receptor ligands. Thus, II was prepared by substitution of (dimethylaminocarbonylhydroxyphenylamino)(ethoxy)cyclobutenedione [preparation given] with (R)-2-amino-N,3-dimethylbutanamide monohydrochloride [preparation given]. Compds. of the invention demonstrated an IC50 value of < 20 μM in CXCR1 SPA assay and < 5 μM in CXCR2 SPA assay. I are useful for the treatment of chemokine-mediated diseases such as acute and chronic inflammatory disorders and cancer.

IT **344-25-2, D-Proline**
RL: RCT (Reactant); RACT (Reactant or reagent)
(stereoselective preparation of disubstituted cyclobutenediones as cxc-chemokine receptor ligands)

RN 344-25-2 HCAPLUS

CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L38 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:414638 HCAPLUS

DOCUMENT NUMBER: 140:406571

TITLE: Preparation of 3,4-di-substituted cyclobutene-1,2-diones as CXC-chemokine receptor ligands

INVENTOR(S): Taveras, Arthur G.; Aki, Cynthia J.; Bond, Richard W.; Chao, Jianping; Dwyer, Michael; Ferreira, Johan A.; Chao, Jianhua; Yu, Younong; Baldwin, John J.; Kaiser, Bernd; Li, Ge; Merritt, J. Robert; Nelson, Kingsley H.; Rokosz, Laura L.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 308 pp., Cont.-in-part of U.S.

Ser. No. 122,841.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004097547	A1	20040520	US 2002-208412	20020730
US 2004106794	A1	20040603	US 2002-241326	20020911
CA 2496676	AA	20040205	CA 2003-2496676	20030730
WO 2004011418	A1	20040205	WO 2003-US23785	20030730
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004147559	A1	20040729	US 2003-630258	20030730
EP 1539678	A1	20050615	EP 2003-772075	20030730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003013109	A	20050621	BR 2003-13109	20030730

PRIORITY APPLN. INFO.:
US 2001-284026P P 20010416
US 2002-122841 A2 20020415
US 2002-208412 A2 20020730
US 2002-241326 A 20020911
WO 2003-US23785 W 20030730

OTHER SOURCE(S): MARPAT 140:406571

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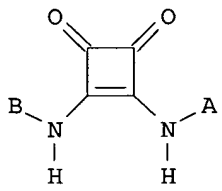

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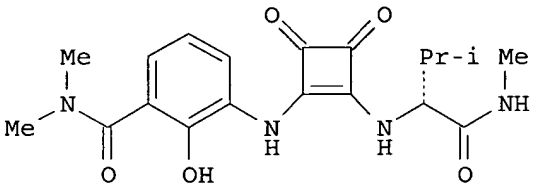


II

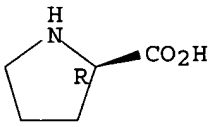
AB Title compds. I [A = (un)substituted heterocycle, heterocyclealkyl, heteroaryl, heteroarylalkyl, cycloalkyl, etc.; B = (un)substituted aryl, heteroaryl, heterocycle, heteroarylarene, etc.], or a pharmaceutically

acceptable salt or solvate thereof, are prepared and disclosed as cxc-chemokine receptor ligands. Thus, II was prepared by substitution of (dimethylaminocarbonylhydroxyphenylamino)(ethoxy)cyclobutenedione [preparation given] with (R)-2-amino-N,3-dimethylbutanamide monohydrochloride [preparation given]. Compds. of the invention demonstrated an IC50 value of < 20 μM in CXCR1 SPA assay and < 5 μM in CXCR2 SPA assay. I are useful for the treatment of chemokine-mediated diseases such as acute and chronic inflammatory disorders and cancer.

IT **344-25-2, D-Proline**
RL: RCT (Reactant); RACT (Reactant or reagent)
(stereoselective preparation of disubstituted cyclobutenediones as cxc-chemokine receptor ligands)

RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L38 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:333705 HCAPLUS
DOCUMENT NUMBER: 140:357355
TITLE: Preparation of diaminothiadiazole dioxides and monoxides as CXC- and CC-chemokine receptor ligands
INVENTOR(S): Taveras, Arthur G.; Chao, Jianhua; Biju, Purakkattle J.; Yu, Younong; Fine, Jay S.; Hipkin, William; Aki, Cynthia J.; Merritt, J. Robert; Li, Ge; Baldwin, John J.; Lai, Gaifa; Wu, Minglang; Hecker, Evan A.
PATENT ASSIGNEE(S): Pharmacopeia, Inc., USA; Schering Corporation; Pharmacopeia Drug Discovery, Inc.
SOURCE: PCT Int. Appl., 540 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004033440	A1	20040422	WO 2003-US31707	20031007
WO 2004033440	C1	20050602		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2501535	AA	20040422	CA 2003-2501535	20031007
US 2004186142	A1	20040923	US 2003-680393	20031007
EP 1551818	A1	20050713	EP 2003-781311	20031007

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.: US 2002-417371P P 20021009
WO 2003-US31707 W 20031007

OTHER SOURCE(S): MARPAT 140:357355

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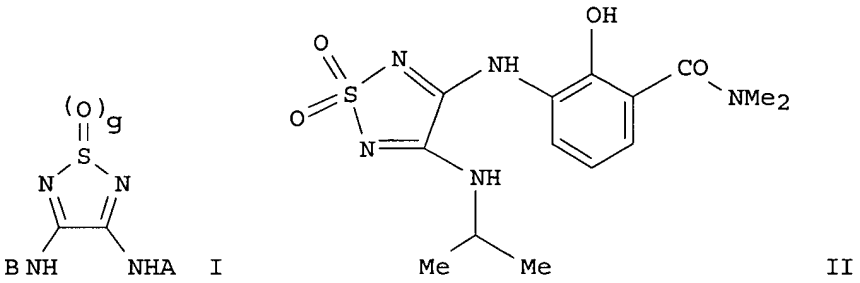
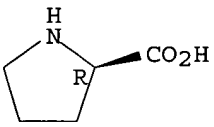


AB Disclosed are diaminothiadiazole mono- and dioxides (shown as I; e.g. II) and the pharmaceutically acceptable salts and solvates thereof. Examples of substituent A include heteroaryl, aryl, heterocycloalkyl, cycloalkyl, aryl, alkynyl, alkenyl, aminoalkyl, alkyl or amino; examples of substituent B include aryl and heteroaryl; g = 1, 2. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and cardiac reperfusion injury, acute pain, acute and chronic inflammatory pain, and neuropathic pain using I. Although the methods of preparation are not claimed, hundreds of example prepns. and/or characterization data are included. For example, II was prepared in 31% yield from the 4-methoxy analog and isopropylamine in the presence of DIEA in MeOH; the 4-methoxy analog was prepared from the dimethoxy analog and N,N-dimethyl-3-amino-2-hydroxybenzamide in 99% crude yield. Antagonist activities of some examples of I towards CXCR1, CXCR2 and CCR7 are given.

IT **344-25-2**, (R)-Pyrrolidine-2-carboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of diaminothiadiazole dioxides and monoxides as CXC- and CC-chemokine receptor ligands)

RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:310947 HCAPLUS

DOCUMENT NUMBER: 140:315651
TITLE: Pharmaceutical compositions for the treatment of autism and similar disorders with oxytocin analogs
INVENTOR(S): Hollander, Eric
PATENT ASSIGNEE(S): PR Pharmaceuticals, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004030524	A2	20040415	WO 2003-US31493	20031003
WO 2004030524	A3	20040610		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2500831	AA	20040415	CA 2003-2500831	20031003
EP 1556068	A2	20050727	EP 2003-770645	20031003
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-415837P P 20021003
WO 2003-US31493 W 20031003

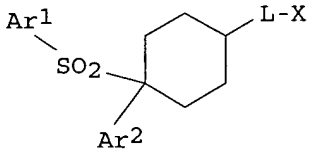
AB Methods of treating certain behavioral characteristics associated with autism are provided. Addnl., methods of treating disorders associated with repetitive behaviors, social deficits and/or cognitive deficits are also provided. A therapeutic amount of oxytocin or oxytocin analogs, either alone or in combination, are administered to individuals demonstrating behavioral characteristics associated with autism or other disorders to reduce the severity of the debilitating behavior. In various aspects, characteristics such as deficit in social awareness or cognitive skills and repetitive behaviors are treated. Co-administration of oxytocin and/or oxytocin analogs with known psychopharmacol. agents is also provided. Advantageously, oxytocin and oxytocin analogs do not have deleterious effects with other drugs such that administration results in few side effects.

L38 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:308409 HCAPLUS
DOCUMENT NUMBER: 140:321108
TITLE: Preparation of aryl cyclohexyl sulfones as γ-secretase inhibitors useful against **Alzheimer**'s disease
INVENTOR(S): Churcher, Ian; Harrison, Timothy; Kerrad, Sonia; Oakley, Paul Joseph; Shaw, Duncan Edward; Teall, Martin Richard; Williams, Susannah
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004031137	A1	20040415	WO 2003-GB4102	20030925
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2500964	AA	20040415	CA 2003-2500964	20030925
EP 1551797	A1	20050713	EP 2003-748306	20030925
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2004122050	A1	20040624	US 2003-679557	20031006
PRIORITY APPLN. INFO.:			GB 2002-23039 A	20021004
			WO 2003-GB4102 W	20030925

OTHER SOURCE(S): MARPAT 140:321108
GI



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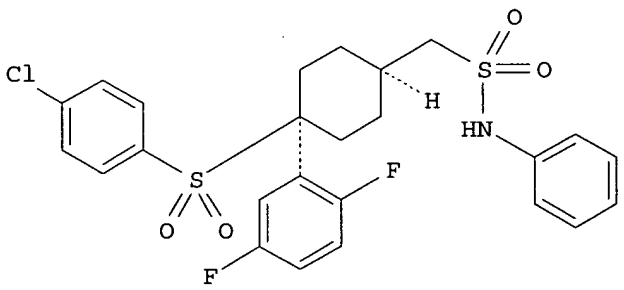


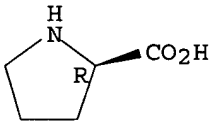
II

AB Aryl cyclohexyl sulfones (shown as I; variables defined below; e.g. II) inhibit the processing of APP by γ-secretase, and hence are useful in treatment of **Alzheimer**'s disease. For I: X = SCN, SR1, S(O)R1, (CRaRb)mSO2R1, SO2N(R2)2, SO2NHCOR1, SO2NHN(R2)2, OSO2N(R2)2, OS(O)N(R2)2, OSO2NHCOR1, COR4, NHCOR1, NHCO2R1, NHCON(R2)2, NHSO2R1 or NHSO2N(R2)2; L = a bond, :CH- or -(CHRa)n- with provisos; n = 1-3; Ar1 and Ar2 = Ph or heteroaryl, either of which bears 0-3 halogen, CN, NO2, CF3, CHF2, OH, OCF3, CHO, CH:NOH, C1-4-alkoxy, C1-4-alkoxycarbonyl, C2-6-acyl, C2-6-alkenyl, and C1-4-alkyl; Ra = H, alkyl; Rb = H, alkyl, CO2H, alkoxycarbonyl, alkylsulfonyl; R1 = CF3, (substituted) alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl(alkyl), heterocyclyl(alkyl); R2 = H, (substituted) alkoxy, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl; R3 = H, alkyl, Ph, heteroaryl; R4 = CRaRbSO2R1, pyridine N-oxide, substituted Ph,

heteroaryl; addnl. details are given in the claims. Although the methods of preparation are not claimed, example prepns. and/or characterization data are included for <180 examples of I and some intermediates. For example, II was prepared from excess aniline and [cis-4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)cyclohexyl]methanesulfonyl chloride, which was prepared from SO2Cl2, KNO3 and [cis-4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)cyclohexyl]methanethiol, which was prepared from in 2 steps from iodo[cis-4-(4-chlorobenzenesulfonyl)-4-(2,5-difluorophenyl)cyclohexyl]methane, which was prepared photochem. from [cis-4-(4-Chlorophenylsulfonyl)-4-(2,5-difluorophenyl)cyclohexyl]acetic acid, iodoisobenzene diacetate and I2. The examples all had an ED50 against γ-secretase of <1 μM, typically <0.5 μM, in most cases <100 nM, and in preferred cases <10 nM.

IT **344-25-2**, (R)-2-Carboxypyrrolidine
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of aryl cyclohexyl sulfones as γ-secretase inhibitors useful against **Alzheimer**'s disease)
RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:142804 HCAPLUS
DOCUMENT NUMBER: 140:199333
TITLE: Preparation of piperazine and piperidine derivatives for treating or preventing neuronal damage or to stimulate nerve growth
INVENTOR(S): Tomlinson, Ronald; Lauffer, David; Mullican, Michael
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 46 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004034019	A1	20040219	US 2002-214906	20020808
PRIORITY APPLN. INFO.:			US 2002-214906	20020808

OTHER SOURCE(S): MARPAT 140:199333
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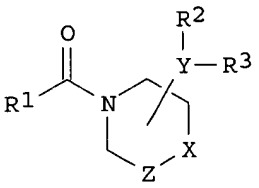

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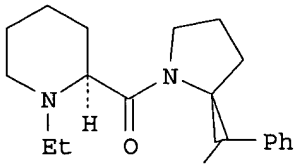


II

AB The authors have prepared a variety of piperidine and piperazine derivs. I [R1 = (un)saturated monocycle, bicycle, tricycle; R2, R3 = independently H, Ar, none, Ar = (un)substituted Ph, 1-naphthyl, pyrazinyl, indolyl, etc.; X = C(R4)2, N, N(R4), O, S, SO, SO2, R4 = independently H, alkyl, alkenyl, alkynyl; Y = O, alkyl, alkenyl, alkynyl; Z = (CH2)n, n = 0, 1, 2] that are useful for treating or preventing neuronal damage, particularly damage associated with neurol. diseases. Thus, the pyrrolidinylpiperidine II was prepared by reacting 1-ethyl-(2S)-piperidine-2-carboxylic acid with (S)-2-(1,1-diphenylmethyl)pyrrolidine. In a neuroprotection assay, II displayed an EC50(nM) greater than 500. The invention also provides pharmaceutical compns. comprising the compds. and methods of utilizing those compns. for treating or preventing neuronal damage or for stimulating nerve growth.

L38 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:60505 HCAPLUS
DOCUMENT NUMBER: 140:128412
TITLE: Preparation of azolidinone-vinyl fused-benzene derivatives for therapeutic uses as PI3 kinase inhibitors
INVENTOR(S): Rueckle, Thomas; Jiang, Xuliang; Gaillard, Pascale; Church, Dennis; Vallotton, Tania
PATENT ASSIGNEE(S): Applied Research Systems Ars Holding N.V., Neth. Antilles
SOURCE: PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

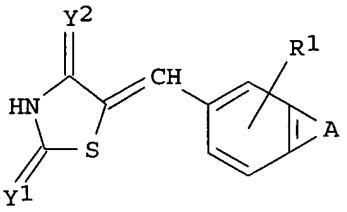
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004007491	A1	20040122	WO 2003-EP50302	20030710
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004092561	A1	20040513	US 2002-289998	20021107
CA 2493843	AA	20040122	CA 2003-2493843	20030710
BR 2003012752	A	20050426	BR 2003-12752	20030710
BR 2003012650	A	20050503	BR 2003-12650	20030710
EP 1549644	A1	20050706	EP 2003-763907	20030710

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.: EP 2002-100798 A 20020710
US 2002-289998 A 20021107
WO 2003-EP50302 W 20030710

OTHER SOURCE(S): MARPAT 140:128412

GI



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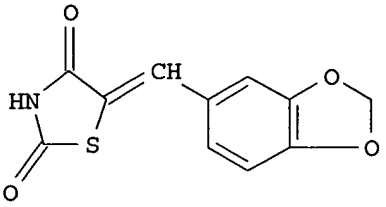


II

AB The present invention is related to the preparation of azolidinedione-vinyl fused-benzene derivs., such as I [R1 = H, CN, carboxy, acyl, alkoxy, halogen, acyloxy, etc.; A = fused heterocyclic or carbocyclic ring; Y1, Y2 = S, O, NH], and their use in pharmaceutical compns. as PI3 kinase (PI3K) inhibitors. These azolidinones are claimed for use in the treatment and/or prophylaxis of autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, cancer, graft rejection, lung injuries, chronic obstructive pulmonary disease, anaphylactic shock, fibrosis, psoriasis, allergic diseases, asthma, stroke or ischemic conditions, ischemia-reperfusion, platelet aggregation/activation, skeletal muscle atrophy/hypertrophy, leukocyte recruitment in cancer tissue, angiogenesis, invasion metastasis in melanoma and Kaposi's sarcoma, sepsis, transplantation, pancreatitis, multi-organ failure, glomerulosclerosis, glomerulonephritis, progressive renal fibrosis, endothelial and epithelial injuries in the lung or in general lung airways inflammation. Further, these azolidinones are claimed for use in the treatment of atherosclerosis, hypertrophy, cardiac myocyte dysfunction, elevated blood pressure, vasoconstriction, **Alzheimer**'s disease, Huntington's disease, CNS trauma, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, thrombosis, and brain infection/inflammation such as meningitis or encephalitis. Thus, azolidinone II was prepared via a condensation reaction of piperonal with 2,4-thiazolidinedione using β-alanine in acetic acid and stirring at 100° for 3 h. Some of the prepared azolidinones were assayed for PI3Kγ inhibition using a high throughput PI3K lipid kinase binding assay. Tablet, capsule, liquid and injectable pharmaceutical compns. were presented.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:972066 HCAPLUS
DOCUMENT NUMBER: 140:27753

TITLE: Preparation of phenylalkyl thiophene-type vitamin D receptor modulators for treating bone disease, psoriasis and other disorders

INVENTOR(S): Dahnke, Karl Robert; Gajewski, Robert Peter; Jones, Charles David; Linebarger, Jared Harris; Lu, Jianliang; Ma, Tianwei; Nagpal, Sunil; Simard, Todd

Parker; Yee, Ying Kwong; Bunel, Emilio Enrique; Stites, Ryan Edward

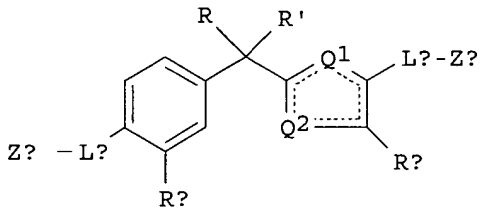
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 504 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003101978	A1	20031211	WO 2003-US14539	20030522
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2485503	AA	20031211	CA 2003-2485503	20030522
BR 2003009983	A	20050222	BR 2003-9983	20030522
EP 1511740	A1	20050309	EP 2003-728782	20030522
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-384151P P 20020529
WO 2003-US14539 W 20030522

OTHER SOURCE(S): MARPAT 140:27753

GI



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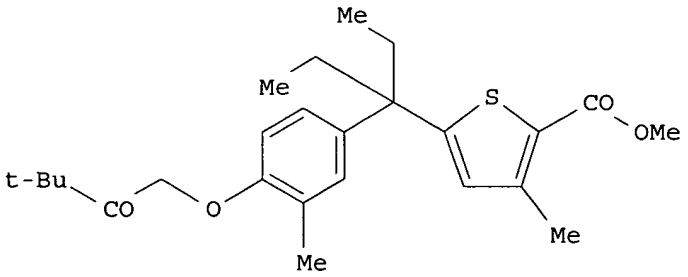


II

AB The present invention relates to novel, nonsecosteroidal, phenylalkyl thiophene compds. (shown as I; variables defined below; e.g. 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-(methoxycarbonyl)-4-(methyl)thiophen-2-yl]pentane (II)) with vitamin D receptor (VDR)

modulating activity that are less hypercalcemic than 1α,25 dihydroxy vitamin D3. These compds. are useful for treating bone disease and psoriasis. For I: R and R' = C1-C5 alkyl, C1-C5 fluoroalkyl, or together R and R' form a (un)substituted, (un)saturated carbocyclic ring having 3-8 C atoms; ring atoms Q1 and Q2 = C or S, with the proviso that one atom is S and the other atom is C; RP and RT = H, halo, C1-C5 alkyl, C1-C5 fluoroalkyl, -O-C1-C5 alkyl, -S-C1-C5 alkyl, -O-C1-C5 fluoroalkyl, -CN, -NO2, acetyl, -S-C1-C5 fluoroalkyl, C2-C5 alkenyl, C3-C5 cycloalkyl, and C3-C5 cycloalkenyl; LP and LT are divalent linking bond, -(CH2)mC(X1)- (X1 = O, S; m = 0-2), -(CH2)mCH(OH)-, etc.; ZP and ZT = H, Ph, benzyl, fluorophenyl, C1-C5 alkyl, etc.; addnl. details including provisos are given in the claims. Although the methods of preparation are not claimed, .apprx.180 example prepns. are included. For example, II was prepared in 7 steps starting from 2-hydroxy-5-bromotoluene and tert-butyldimethylsilyl chloride and involving intermediates 2-(tert-Butyldimethylsilyloxy)-5-bromotoluene, 3'-[4-(tert-Butyldimethylsilyloxy)-3-methylphenyl]pentan-3-ol, 3'-[4-(Hydroxy)-3-methylphenyl]-3'-[4-(methyl)thiophen-2-yl]pentane, 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[4-(methyl)thiophen-2-yl]pentane, 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[5-(methoxycarbonyl)-4-(methyl)thiophen-2-yl]pentane, and 3'-[4-(Hydroxy)-3-methylphenyl]-3'-[5-(methoxycarbonyl)-4-(methyl)thiophen-2-yl]pentane with yields of 97, 72, 95, 92, 54, 100 and 85, resp. Results are tabulated for many of the example I for the following assays: RXR-VDR heterodimerization (SaOS-2 cells), VDR co-transfection (Caco-2 cells), osteocalcin promotor, mouse hypercalcemia, keratinocyte proliferation, and IL-10 induction; e.g. one enantiomer of 1-[4-[1-ethyl-1-(5-hydroxymethyl-4-methylthiophen-2-yl)propyl]-2-methylphenoxy]-3,3-dimethylbutan-2-ol exhibits an EC50 = 2.8 nM in the RXR-VDR assay compared to 3 nM for the control calcipotriol.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

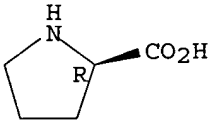
L38 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:805768 HCAPLUS
DOCUMENT NUMBER: 139:286331
TITLE: Antitumor agents comprising D-amino acid oxidase and its substrates
INVENTOR(S): Sawa, Tomohiro; Akaike, Takaki; Maeda, Hiroshi
PATENT ASSIGNEE(S): Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003292457	A2	20031015	JP 2002-101168	20020403
PRIORITY APPLN. INFO.:			JP 2002-101168	20020403

AB Antitumor agents comprise (1) synthetic polymer-bound D-amino acid oxidase and (2) D-amino acids for sequential administration. The antitumor agents locally produce active H2O2 which shows selective activities in the tumor site.

IT **344-25-2, D-Proline**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor agents comprising D-amino acid oxidase and its substrates)
RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



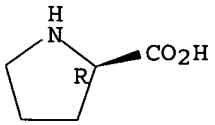
L38 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:18965 HCAPLUS
DOCUMENT NUMBER: 138:202962
TITLE: Mutational analysis of the structural organization of polyglutamine aggregates
AUTHOR(S): Thakur, Ashwani K.; Wetzel, Ronald
CORPORATE SOURCE: Graduate School of Medicine, University of Tennessee Medical Center, Knoxville, TN, 37920, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(26), 17014-17019
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The formation of **amyloid**-like aggregates by expanded polyglutamine (polyGln) sequences is suspected to play a critical role in the neuropathol. of Huntington's disease and other expanded CAG-repeat diseases. To probe the folding of the polyGln sequence in the aggregate, we replaced Gln-Gln pairs at different sequence intervals with Pro-Gly pairs, elements that are compatible with β-turn formation and incompatible with β-extended chain. We find that PGQ9 and PGQ10, peptides consisting of four Q9 or Q10 elements interspersed with PG elements, undergo spontaneous aggregation as efficiently as a Q45 sequence, whereas the corresponding PGQ7 and PGQ8 peptides aggregate much less readily. Furthermore, a PDGQ9 sequence containing **D-prolines** aggregates more efficiently than the peptide with L-prolines, consistent with β-turn formation in aggregate structure. Introduction of one addnl. Pro residue in the center of a Q9 element within PGQ9 completely blocks the peptide's ability to aggregate. This strongly suggests that the Q9 elements are required to be in extended chain for efficient aggregation to occur. We determined the critical nucleus for aggregation nucleation of the PGQ9 peptide to be one, a result identical to that for unbroken polyGln sequences. The PGQN peptide aggregates are structurally quite similar to Q45 aggregates, as judged by heterologous seeding aggregation kinetics, recognition by an anti-polyGln aggregate antibody, and electron microscopy. The results suggest that polyGln aggregate structure consists of alternating elements of extended chain and turn. In the future it should be possible to conduct detailed and interpretable mutational studies in the PGQ9 background.

IT **344-25-2, D-Proline**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(aggregates; PDGQ9 sequence containing **D-prolines** aggregates more efficiently than the peptide with L-prolines, consistent with β-turn formation in aggregate structure)

RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:849596 HCAPLUS
DOCUMENT NUMBER: 137:370353
TITLE: Preparation of spiropiperidine derivatives, nociceptin receptor antagonists containing the same as the active ingredient, and medicinal compositions
INVENTOR(S): Sagara, Takeshi; Itoh, Satoru; Nakashima, Hiroshi; Goto, Yasuhiro; Shimizu, Atsushi; Iwasawa, Yoshikazu; Okamoto, Osamu
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088089	A1	20021107	WO 2002-JP3878	20020418

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2001-121543 A 20010419
OTHER SOURCE(S): MARPAT 137:370353
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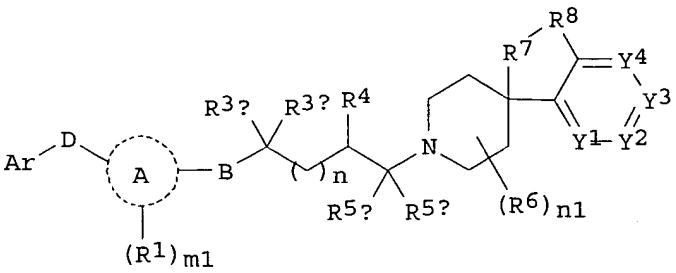

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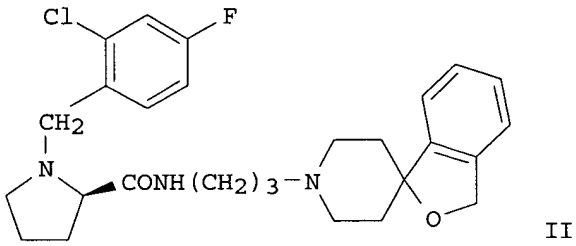

II

AB Spiropiperidine derivs. typified by compds. represented by the general formula (I) or pharmacol. acceptable salts thereof [wherein the ring A = 3- to 6-membered monocyclic aromatic or aliphatic ring optionally containing 1 or ≥2 heteroatoms selected from N, O, and S; B = CONH, NHCO; D = a single bond, O, S, CO, (un)substituted CH2 or CH2CH2; R1 = HO, halo, mono or di(lower alkyl)amino, lower alkylsulfonyl, lower alkylsulfinyl, optionally F-substituted lower alkoxy, lower alkylcarbonyloxy, lower alkylcarbonylamino, (un)substituted lower alkyl; m1 = an integer of 0-4; n = 0,1; R3a, R3b, R5a, R5b = H, halo, C1-3 alkyl, C1-3 haloalkyl; R4 = H, halo, HO, C1-3 alkyl, C1-3 haloalkyl; or R5a and R5b together form CH2, CH2CH2, or (CH2)3; R6 = halo, C1-3 alkyl; m = an integer of 0-8; R7, R8 = O, CH2; or R7 and R8 together form CH:CH; provided that R7 and R8 are not simultaneously O; Ar = (un)substituted mono- or bicyclic aryl or heteroaryl; Y1-Y4 = (un)substituted CH, N; provided that ≥2 of Y1-Y4 are not simultaneously N]. These compds. have an antagonistic effect on the binding of nociceptin to a nociceptin receptor ORL1 at an extremely low concentration, which makes them useful as analgesics for cancer pain and diseases in associated with pain, antagonists to narcotic analgesic-tolerance, antagonists to narcotic analgesic -addiction or withdrawal syndrome, analgesic potentiators, antiobesity agents, brain function improving agents, and remedies for **Alzheimer**'s disease, dementia, schizophrenia, Parkinson's disease, Huntington's chorea, depression, diabetes insipidus, polyuria, and hypotension. Thus, to a solution of N-[3-[spiro[isobenzofuran-1(3H),4'-piperidine]-1-yl]propyl]-D-prolinamide dihydrochloride in DMF were added 2-chloro-4-fluorobenzaldehyde and sodium triacetoxyborohydride successively and stirred at room temperature for 4 h to give 1-(2-chloro-4-fluorobenzyl)-N-[3-spiro[isobenzofuran-1(3H),4'-piperidine]-1-ylpropyl]-D-prolinamide (II). II showed IC50 of 0.043 nM for inhibiting the binding of [125I]Tyr14-nociceptin to a membrane preparation obtained from CHO cells transfected with human nociceptin gene.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:814089 HCAPLUS
DOCUMENT NUMBER: 137:325178
TITLE: Preparation of 3,4-di-substituted cyclobutene-1,2-diones as cxc-chemokine receptor ligands
INVENTOR(S): Taveras, Arthur G.; Aki, Cynthia J.; Bond, Richard W.; Chao, Jianping; Dwyer, Michael; Ferreira, Johan A.; Chao, Jianhua; Yu, Younong; Baldwin, John J.; Kaiser, Bernd; Li, Ge; Merritt, J. Robert; Nelson, Kingsley H.; Rokosz, Laura L.
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia, Inc.
SOURCE: PCT Int. Appl., 394 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083624	A1	20021024	WO 2002-US12681	20020415
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2444031	AA	20021024	CA 2002-2444031	20020415
NZ 529551	A	20031219	NZ 2002-529551	20020415
EP 1381590	A1	20040121	EP 2002-739172	20020415
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002008957	A	20040622	BR 2002-8957	20020415
CN 1516687	A	20040728	CN 2002-811979	20020415
JP 2004532846	T2	20041028	JP 2002-581381	20020415
ZA 2003007905	A	20050110	ZA 2003-7905	20031009
NO 2003004612	A	20031208	NO 2003-4612	20031015
PRIORITY APPLN. INFO.:			US 2001-284026P P	20010416
			WO 2002-US12681 W	20020415

OTHER SOURCE(S): MARPAT 137:325178
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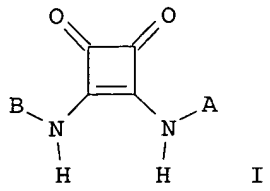

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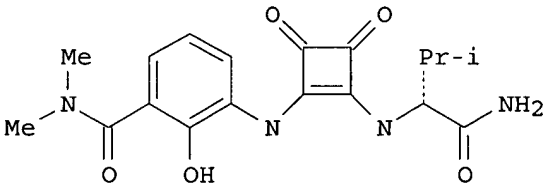


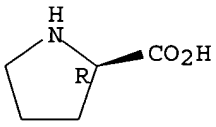
II

AB Title compds. I [A = (un)substituted heterocycle, heterocyclealkyl, heteroaryl, heteroarylalkyl, cycloalkyl, etc.; B = (un)substituted aryl, heteroaryl, heterocycle, heteroarylarene, etc.], or a pharmaceutically acceptable salt or solvate thereof, are prepared and disclosed as cxc-chemokine receptor ligands. Thus, II was prepared by substitution of (dimethylaminocarbonylhydroxyphenylamino)(ethoxy)cyclobutenedione [preparation given] with (R)-2-amino-N,3-dimethylbutanamide monohydrochloride [preparation given]. Compds. of the invention demonstrated an IC50 value of < 20 μM in CXCR1 SPA assay and < 5 μM in CXCR2 SPA assay. I are useful for the treatment of chemokine-mediated diseases such as acute and chronic inflammatory disorders and cancer.

IT **344-25-2, D-Proline**
RL: RCT (Reactant); RACT (Reactant or reagent)
(stereoselective preparation of disubstituted cyclobutenediones as cxc-chemokine receptor ligands)

RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:66366 HCAPLUS
DOCUMENT NUMBER: 136:303268
TITLE: Enantioseparation of amino acids on a polysaccharide-based chiral stationary phase
AUTHOR(S): Ye, Yun K.; Lord, Barbara S.; Yin, Li; Stringham, Rodger W.
CORPORATE SOURCE: Chemical Process Research and Development, Chambers Works, DuPont Pharmaceutical Company, Deepwater, NJ, 08023-0999, USA

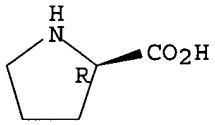
SOURCE: Journal of Chromatography, A (2002), 945(1-2), 147-159
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sulfonic acids are more effective than the commonly used trifluoroacetic acid (TFA) in the chiral resolution of underivatized aromatic amino acids on an **amylosic** column. Sulfonic acid additives give a more UV transparent mobile phase, possibly allowing the detection of nonarom. analytes. Work presented demonstrates that through the combination of sulfonic acid mobile phase additives, amine mobile phase additives and solvent modifier variations, the enantiomers of 20 of 25 probe amino acids are fully resolved, four are partially resolved with only one failing to be separated on a common **amylosic** column.

IT **344-25-2, D-Proline**
RL: ANT (Analyte); ANST (Analytical study)
(enantiosepn. of amino acids by HPLC on a polysaccharide-based chiral stationary phase)

RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

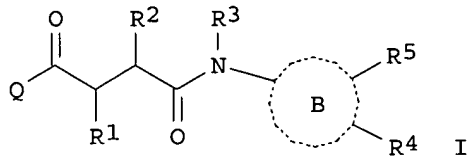


REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

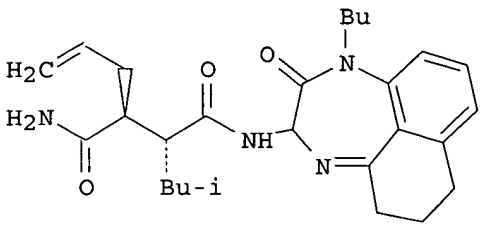
L38 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:618005 HCAPLUS
DOCUMENT NUMBER: 135:195579
TITLE: Preparation and activity of succinoylamino carbocycles and heterocycles as inhibitors of aβ protein production
INVENTOR(S): Olson, Richard E.; Maduskuie, Thomas P.; Thompson, Lorin Andrew; Tebben, Andrew J.; Wang, Nenghui; Deng, Wei; Liu, Hong
PATENT ASSIGNEE(S): Dupont Pharmaceuticals Company, USA
SOURCE: PCT Int. Appl., 236 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060826	A2	20010823	WO 2001-US5236	20010216
WO 2001060826	A3	20020117		
W: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
CA 2395862	AA	20010823	CA 2001-2395862	20010216
US 2002055501	A1	20020509	US 2001-788227	20010216

US 6525044 B2 20030225
EP 1261610 A2 20021204 EP 2001-914400 20010216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR
JP 2003523345 T2 20030805 JP 2001-560210 20010216
PRIORITY APPLN. INFO.: US 2000-183186P P 20000217
WO 2001-US5236 W 20010216
OTHER SOURCE(S): MARPAT 135:195579
GI



I



II

AB Synthesis of succinoylamino carbocycles and heterocycles (I) [Q = (un)substituted OH, NH2; R1 = (un)substituted alkyl, alkenyl; R2 = (un)substituted alkyl; R3 = H, alkyl; R4 = (un)substituted aryl; R5 = (un)substituted OH, (un)substituted CONH2, (un)substituted alkyl; B = nitrogen heterocycle fused by one or more (un)substituted (un)saturated carbocyclic or heterocyclic rings] having drug and bio-affecting properties, their pharmaceutical compns. and methods of use is disclosed. Thus, (II) was prepared by amidation of 2-amino-3-oxo-2,3,4,8,9,10-hexahydronaphtho[1,8-ef]diazepine with tert-Bu (2R,3S)-3-allyl-2-isobutylsuccinic acid followed by aminolysis and butylation. II inhibits production of β- **amyloid** protein with an IC50 < 100υM in an immunopptn. assay using N9 cells characterized for expression of exogenous **amyloid** precursor protein. These novel compds. inhibit the processing of **amyloid** precursor protein and, more specifically, inhibit the production of Aβ-peptide, thereby acting to prevent the formation of neurol. deposits of **amyloid** protein. More particularly, the present invention relates to the treatment of neurol. disorders related to β- **amyloid** production such as **Alzheimer**'s disease and Down's Syndrome.

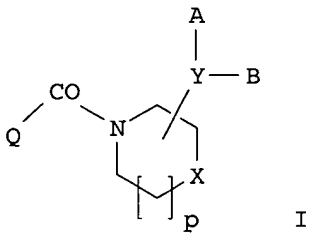
L38 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:597978 HCAPLUS
DOCUMENT NUMBER: 135:166844
TITLE: Preparation of piperazinyl and piperidinyl ketones useful for treating or preventing neuronal damage and for stimulating nerve growth
INVENTOR(S): Tomlinson, Ronald; Lauffer, David; Mullican, Michael
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA

SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001058891	A2	20010816	WO 2001-US4210	20010209
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2398822	AA	20010816	CA 2001-2398822	20010209
EP 1257544	A2	20021120	EP 2001-912714	20010209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001008175	A	20030128	BR 2001-8175	20010209
JP 2003522767	T2	20030729	JP 2001-558441	20010209
EE 200200442	A	20031215	EE 2002-442	20010209
NZ 520638	A	20040528	NZ 2001-520638	20010209
ZA 2002005933	A	20030724	ZA 2002-5933	20020724
NO 2002003787	A	20021011	NO 2002-3787	20020809

PRIORITY APPLN. INFO.:
US 2000-181944P P 20000211
US 2000-247330P P 20001110
WO 2001-US4210 W 20010209

OTHER SOURCE(S): MARPAT 135:166844
GI



I

AB The present invention relates to piperazine and piperidine derivs. I (e.g. 1-[(S)-2-(1,1-diphenylmethyl)pyrrolidin-1-yl]-1-((S)-1-ethylpiperidin-2-yl)methanone), which are especially useful for treating or preventing neuronal damage, particularly damage associated with neurol. diseases. These compds. are also useful for stimulating nerve growth. The invention also provides compns. comprising the compds. of the present invention and methods of using those compns. for treating or preventing neuronal damage or for stimulating nerve growth. In I, each Q is a monocyclic, bicyclic or tricyclic ring system wherein in said ring system: a. each ring is independently partially unsatd. or fully saturated; b. each ring comprises 3 to 7 ring atoms independently = C, N, O or S; c. ≤4 ring atoms in Q are selected from N, O or S; d. any S is optionally replaced with S(O) or S(O)2; e. at least one ring comprises a N ring atom that is substituted

with R1; f. 1-5 H atoms in Q are optionally and independently replaced with halo, -OH, :O, :N-OR1, (C1-C6)-straight or branched alkyl, Ar-substituted-(C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, Ar-substituted-(C2-C6)-straight or branched alkenyl or alkynyl, O-(C1-C6)-straight or branched alkyl, O-[(C1-C6)-straight or branched alkyl]-Ar, O-(C2-C6)-straight or branched alkenyl or alkynyl, O-[(C2-C6)-straight or branched alkenyl or alkynyl]-Ar, or O-Ar; and g. Q is not an indole or a pyroglutamic moiety. Each R1 is independently selected from (C1-C6)-straight or branched alkyl, Ar-substituted-(C1-C6)-straight or branched alkyl, cycloalkyl-substituted-(C1-C6) straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar-substituted-(C2-C6)-straight or branched alkenyl or alkynyl. One to two CH2 groups of said alkyl, alkenyl, or alkynyl chains in R1 are optionally and independently replaced with O, S, S(O), S(O)2, C(O) or N(R2), wherein when R1 is bound to N, the CH2 group of R1 bound directly to said N cannot be replaced with C(O). Ar = Ph, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyraxolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,2,3-thiadiazolyl, benzoxazolyl, pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, or any other chemical feasible monocyclic or bicyclic ring system, wherein each ring consists of 5 to 7 ring atoms and wherein each ring comprises 0 to 3 heteroatoms independently selected from N, O, or S. Each Ar is optionally and independently substituted with 1-3 substituents selected from halo, hydroxy, nitro, -SO3H, :O, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, O-[(C1-C6)-straight or branched alkyl], O-[(C1-C6)-straight or branched alkenyl], O-benzyl, O-Ph, 1,2-methylenedioxy, -(R3)(R4), carboxy, N-(C1-C6-straight or branched alkyl or C2-C6-straight or branched alkenyl) carboxamides, N,N-di(C1-C6-straight or branched alkyl or C2-C6-straight or branched alkenyl) carboxamides, N-(C1-C6-straight or branched alkyl or C2-C6-straight or branched alkenyl) sulfonamides, or N,N-di(C1-C6-straight or branched alkyl or C2-C6-straight or branched alkenyl) sulfonamides. Each of R3 and R4 = (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, H, Ph or benzyl; or wherein R3 and R4 are taken together with the N atom to which they are bound to form a 5-7 membered heterocyclic ring. Each R2 = H, (C1-C6) straight or branched alkyl, or (C2-C6)-straight or branched alkenyl or alkynyl. X = C(R2)2, N, N(R2), O, S, S(O), or S(O)2. Y = a bond, -O-, (C1-C6)-(straight or branched) alkyl, or (C2-C6)-(straight or branched) alkenyl or alkynyl; wherein Y is bonded to the depicted ring via a single bond or a double bond; and wherein one to two of the CH2 groups of said alkyl, alkenyl, or alkynyl is optionally and independently replaced with O, S, S(O), S(O)2, C(O) or N(R). P = 0-2; each of A and B is independently selected from H or Ar; or one of A or B is absent; and wherein two C ring atoms in the depicted ring structure may be linked to one another via a C1-C4 straight alkyl or a C2-C4 straight alkenyl to create a bicyclic moiety. Results of a neuroprotection assay are tabulated for about 150 of the claimed compds. About 70 example prepns. are included.

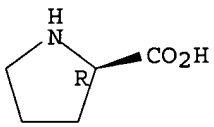
L38 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:894535 HCAPLUS

DOCUMENT NUMBER: 134:291652
TITLE: Characterization of betabellins 15D and 16D, designed beta-sandwich proteins that have **amyloidogenic** properties
AUTHOR(S): Lim, Amareth; Makhov, Alexander M.; Connors, Lawreen H.; Bond, Jeremy; Inouye, Hideyo; Griffith, Jack D.; Kirschner, Daniel A.; Costello, Catherine E.; Erickson, Bruce W.
CORPORATE SOURCE: Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA
SOURCE: Peptides for the New Millennium, Proceedings of the American Peptide Symposium, 16th, Minneapolis, MN, United States, June 26-July 1, 1999 (2000), Meeting Date 1999, 22-23. Editor(s): Fields, Gregg B.; Tam, James P.; Barany, George. Kluwer Academic Publishers: Dordrecht, Neth.
CODEN: 69ATHX
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The betabellin structure is a β-sandwich protein consisting of two 32-residue β-sheets packed against one another by hydrophobic interactions. D-Amino acid residues are used to favor formation of type-I' β-turns. The amino acid sequence of betabellin 15S (B15S) contains a conformationally constrained D-Pro residue at the i + 1 position of each type-I' β turn. To test if a D-Pro residue is necessary at this position, the three D-Pro residues of B15S were replaced by D-Ala residues in B16S. Air oxidation of B15S furnishes betabellin 15D (B15D), a 64-residue, disulfide-bridged protein. B15D forms unbranched, multimeric fibrils with each fibril having a diameter of 3.5 nm in folding conditions as revealed by electron microscopy. Similarly, B16D forms unbranched fibrils that associate into ribbons. It was investigated further whether B15D and B16D have other properties associated with **amyloidogenic** proteins. Findings show that both B15D and B16D have unbranched fibrils that stain with Congo red and display a green birefringence. The fibrils of B15D exhibit a cross-β structure. These properties are characteristic of **amyloid** proteins. Both B15D and B16D may provide useful models for studying the mechanism of fibril formation and for designing its potential inhibitors.

IT **344-25-2, D-Proline**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(functional role; characterization of betabellins 15D and 16D, designed beta-sandwich proteins that have **amyloidogenic** properties)
RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:861490 HCAPLUS

DOCUMENT NUMBER: 134:25357
TITLE: Phenyl urea IL-8 receptor antagonists for therapeutic use
INVENTOR(S): Palovich, Michael R.; Widdowson, Katherine L.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000072845	A1	20001207	WO 2000-US14661		20000526
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2375683	AA	20001207	CA 2000-2375683		20000526
BR 2000010843	A	20020219	BR 2000-10843		20000526
EP 1180028	A1	20020220	EP 2000-936369		20000526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
TR 200103448	T2	20020621	TR 2001-200103448		20000526
JP 2003500447	T2	20030107	JP 2000-620957		20000526
AU 766082	B2	20031009	AU 2000-51691		20000526
NZ 514729	A	20031128	NZ 2000-514729		20000526
US 6566387	B1	20030520	US 2001-9212		20011108
ZA 2001009628	A	20021122	ZA 2001-9628		20011122
NO 2001005775	A	20011127	NO 2001-5775		20011127
PRIORITY APPLN. INFO.:			US 1999-136717P	P	19990528
			WO 2000-US14661	W	20000526

OTHER SOURCE(S): MARPAT 134:25357
AB The invention discloses the use of Ph ureas in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8). Preparation of compds. of the invention is described.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:113711 HCAPLUS
DOCUMENT NUMBER: 130:153985
TITLE: Preparation of N-sulfonylprolylphenylalanine derivatives and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
INVENTOR(S): Thorsett, Eugene D.; Semko, Christopher M.; Pleiss, Michael A.; Lombardo, Louis John; Konradi, Andrei W.; Grant, Francine S.; Dressen, Darren B.; Dappen, Michael S.
PATENT ASSIGNEE(S): Athena Neurosciences, Inc., USA; American Home Products Corporation
SOURCE: PCT Int. Appl., 172 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906436	A1	19990211	WO 1998-US15327	19980731
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2291473	AA	19990211	CA 1998-2291473	19980731
AU 9885851	A1	19990222	AU 1998-85851	19980731
EP 1001975	A1	20000524	EP 1998-937054	19980731
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9811573	A	20000919	BR 1998-11573	19980731
JP 2001512138	T2	20010821	JP 2000-505191	19980731
US 6362341	B1	20020326	US 1998-127601	19980731
NO 2000000414	A	20000328	NO 2000-414	20000127
US 2003065193	A1	20030403	US 2002-43275	20020114
US 6586602	B2	20030701		

PRIORITY APPLN. INFO.:	US 1997-112007P	P	19970731
	US 1997-112007P	P	19970731
	US 1997-903585	A1	19970731
	US 1998-127601	A1	19980731
	WO 1998-US15327	W	19980731

OTHER SOURCE(S): MARPAT 130:153985

AB Disclosed are title compds. R1SO2NR2CHR3QCHR5COR6 [R1 = (un)substituted alkyl, (un)substituted aryl, (un)substituted cycloalkyl, (un)substituted heterocyclyl; R2NCHR3 form saturated heterocyclic group with the proviso that when monosubstituted, the substituent on the saturated heterocyclic group is not CO2H; R5 = (CH2)n-aryl, (CH2)n-heteroaryl; n = 1-4; Q = C(X)NR7; R7 = H, alkyl; X = O, S; R6 = NH2, (un)substituted alkoxy, (un)substituted cycloalkoxy, succinimidyloxy, adamantylamino, β-cholest-5-en-3-yloxy, NHOY, NH(CH2)pCO2Y, OCH2NR9R10; Y = H, (un)substituted alkyl, (un)substituted aryl; p = 1-8; R9 = (un)substituted CO-aryl; R10 = H, CH2CO2R11, NHSO2Z; R11 = alkyl; Z = (un)substituted alkyl, (un)substituted cycloalkyl, (un)substituted aryl, (un)substituted heteroaryl, (un)substituted heterocyclyl; and pharmaceutically acceptable salts thereof, with the proviso that when R1 = 2,4,6-Me3C6H2, R2NCHR3 = pyrrolidinyl ring and Q = C(O)NH, then R5 ≠ benzyl; with the further proviso that when R1 = 4-MeC6H4, R2NCHR3 = pyrrolidinyl derived from **D-proline**, and Q = C(O)NH, then R5 ≠ benzyl derived from D-phenylalanine] which bind VLA-4 (also referred to as integrin α4β1 and CD49d/CD29). Certain of these compds. also inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. Such compds. are useful in the treatment of inflammatory diseases in a mammalian patient, e.g., human, wherein the disease may be, for example, asthma, **Alzheimer**'s disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. The compds. can also be administered for the treatment of inflammatory brain diseases such as multiple sclerosis. Thus, BOP-mediated coupling of Boc-L-Pro-OH with L-phenylalanine benzyl ester hydrochloride in the presence of N-methylmorpholine, followed by acidic deprotection, sulfonylation with MeSO2Cl, and catalytic deprotection to give desired dipeptide MeSO2-L-Pro-L-Phe-OH.

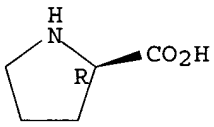
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:12304 HCAPLUS
DOCUMENT NUMBER: 130:66800
TITLE: Preparation of D-amino acid derivatives as cysteine and serine protease inhibitors
INVENTOR(S): Chatterjee, Sankar
PATENT ASSIGNEE(S): Cephalon, Inc., USA
SOURCE: U.S., 43 pp., Cont.-in-part of U.S. Ser. No. 755,839,abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5852007	A	19981222	US 1997-795546	19970206
PRIORITY APPLN. INFO.:			US 1996-755839	B2 19961126

OTHER SOURCE(S): MARPAT 130:66800
AB The compds. QC*(NR2R3)(R4)CONHC(R1)(R5)C(W1)(W2)Y [C* = carbon atom having a D-configuration; Q = GB(CHR20)q; R20 = H, alkyl; q = 0 -2; B = CO, etc.; G = aryl, etc.; R1 = H, alkyl, etc.; R2 = COR6, etc.; R6 = aryl, etc.; R3 = H, alkyl, etc.; further details on R2, R3, Q are given; R4, R5 = H, alkyl; W1 and W2 are selected such that W1 is H and W2 is O(CO)NHR26 where R26 is alkyl, or W1 and W2 are both alkoxy, or W1 is OH and W2 is selected from aralkyl, aralkyloxy, etc.; further details on W1 and W2 are given; Y = H, CH:N2, etc.; further details on Y and R1 are given] are prepared Compds. of this invention in vitro showed IC50 values of 3 - 1000 nM against calpain I.
IT **344-25-2, D-Proline**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of D-amino acid derivs. as cysteine and serine protease inhibitors)
RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



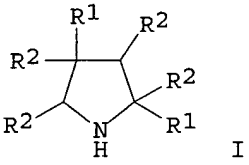
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:194875 HCAPLUS
DOCUMENT NUMBER: 116:194875
TITLE: Preparation of cis- and trans-4-carboxyprolines as L-glutamate transport inhibitors
INVENTOR(S): Chamberlin, A. Richard; Bridges, Richard J.; Cotman, Carl W.; Stanley, Mark S.
PATENT ASSIGNEE(S): University of California, Berkeley, USA

SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9106536	A1	19910516	WO 1990-US6089	19901024
W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2069912	AA	19910426	CA 1990-2069912	19901024
AU 9067393	A1	19910531	AU 1990-67393	19901024
EP 497895	A1	19920812	EP 1990-917026	19901024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05508147	T2	19931118	JP 1990-515858	19901024
US 5942537	A	19990824	US 1993-104417	19930809
PRIORITY APPLN. INFO.:			US 1989-427235 A	19891025
			WO 1990-US6089 A	19901024

OTHER SOURCE(S): MARPAT 116:194875
GI



I

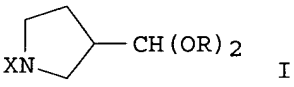
AB Title compds. I [R1 = HO2C, (HO)2P(O), HO3S, R3O2C, (R3O)2P(O), RO3S, (R3O)(HO)P(O), R3NHCO; R3 = (substituted) alkyl; R2 = R3O, (R3)2N, (substituted) alkyl] are prepared N-CBZ-trans-4-hydroxy-L-proline was converted to the cis-Et ester, to this and pyridine in CHCl3 was added 4-ClC6H4SO2Cl to give the cis-tosylate in which NaCN was suspended to give the trans-cyano derivative to which in MeOH was added HCl/MeOH. After 4 days the reaction was quenched with NaHCO3 to give the trans-di-Me ester, which was treated with 4N NaOH to give the free acid, which was deprotected by hydrogenation over Pd/C to give trans-4-carboxy-L-proline (II). In test for L-glutamate blockers, II reduced 3H-glutamate uptake to 45% of control when it was included in the transport assay at 10 μM. The extent of this inhibition was greater than that observed with either D-aspartate, DL-β-threo-hydroxyaspartate or dihydrokainate.

L38 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:164802 HCAPLUS
DOCUMENT NUMBER: 114:164802
TITLE: Preparation and formulation of N-acylprolinal acetals as psychoanaleptic agents
INVENTOR(S): Shioiri, Takayuki; Hamada, Yasumasa; Irako, Naoko; Kado, Kunio
PATENT ASSIGNEE(S): Yakult Honsha Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 384341	A2	19900829	EP 1990-103123	19900219
EP 384341	A3	19911127		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL				
JP 02218663	A2	19900831	JP 1989-38179	19890220
US 5158970	A	19921027	US 1990-476698	19900208
CA 2010035	AA	19900820	CA 1990-2010035	19900214
CA 2010035	C	19980414		

PRIORITY APPLN. INFO.: JP 1989-38179 A 19890220
OTHER SOURCE(S): MARPAT 114:164802
GI



I

AB The title compds. (I; R = alkyl; X = N-protective group, N-protected amino acid-derived acyl), prolyl endopeptidase inhibitors, were prepared Thus, L-prolinal di-Et acetal hydrochloride was stirred 2 h at .apprx.0° and 45 min at room temperature with benzyloxycarbonyl-L-proline in CH2Cl2 containing 1-hydroxybenzotriazole and DCC to give I (R = Et, X = N-benzyloxycarbonyl-L-prolyl) which increased step-down latency of scopolamine-treated rats from 1.0 to 2.0 (no units given) at 1 mg/kg orally.

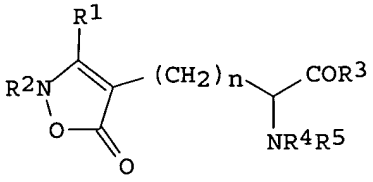
L38 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:632059 HCAPLUS
DOCUMENT NUMBER: 113:232059
TITLE: Preparation of acylpyroglutamates and isoxazolylalanines and analogs as biological memory enhancers
INVENTOR(S): Harada, Setsuo; Nagaoka, Akinobu; Itoh, Katsumi; Terao, Shinji
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 367393	A2	19900509	EP 1989-309430	19890918
EP 367393	A3	19910327		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 03173864	A2	19910729	JP 1989-235123	19890911
US 5021439	A	19910604	US 1989-408389	19890918

PRIORITY APPLN. INFO.: JP 1988-276919 A 19881031
JP 1989-95595 A 19890414

JP 1989-222241 A 19890829
JP 1989-235123 A 19890911

OTHER SOURCE(S): MARPAT 113:232059
GI



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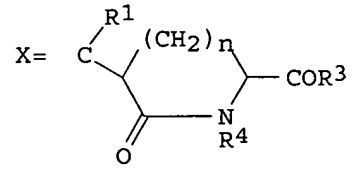
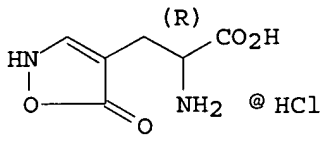


II



III

AB The title compds. [I and II; R1 = H, C-connected organic residue; R2 = H, protecting group; R3 = H, ester or amide residue; R4, R5 = H, acyl, (aryl-substituted) hydrocarbyl; NR4R5 = ring, (substituted) benzylidene; X = O, NOH; n = 0-3], were prepared Thus, Me (R)-N-tert-butoxycarbonylpyroglutamate in THF at -78° was treated with LiN(CHMe2)2 and then HCO2CHMe2 to give 29% II (R1 = H, R3 = OMe, R4 = Me3CO2C, X = O, n = 1). The latter was oximated and then treated successively with NaOH in MeOH, aqueous NaOH, and HCl/dioxane to give title isoxazolone III. III at 10 mg/kg i.p. in mice increased latency in a light-dark shock test from 100% (cycloheximide-impaired controls) to 278%. Tablet and injection formulations of III.Na are given.

L38 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:94948 HCAPLUS
DOCUMENT NUMBER: 108:94948
TITLE: Preparation of vasopressin fragment derivatives as nootropics for treatment of senility
INVENTOR(S): Goto, Giichi; Nagaoka, Akinobu; Wakimasu, Mitsuhiro
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd. , Japan
SOURCE: Eur. Pat. Appl., 68 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 227410	A2	19870701	EP 1986-309800	19861216
EP 227410	A3	19890208		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4748154	A	19880531	US 1986-939103	19861208
CA 1292841	A1	19911203	CA 1986-525277	19861215
JP 62234095	A2	19871014	JP 1986-302660	19861218
JP 08030079	B4	19960327		

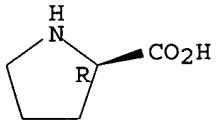
PRIORITY APPLN. INFO.: JP 1985-291474 A 19851224
OTHER SOURCE(S): CASREACT 108:94948
AB PGlu-Asp(NHR1)-Cys(H-Cys-OH)-A-D-Lys-B [I; R1 = H, C1-18 alkyl,

(substituted) phenyl-C1-3 alkyl; A = amino, C1-6 alkylaminoacid residue; B = OH, amino, amino acid or amide] were prepared as vasopressin fragment peptides, useful for treatment and prevention of dementia. PGlu-Asn-Cys(H-Cys-OH)-Pro-D-Lys-OH (II) was prepared using solution-phase methods, starting from BOC-D-Lys(Z)-OH.DCHA (BOC = tert-butyoxycarbonyl, Z = benzyloxycarbonyl, DCHA = dicyclohexylamine). II reversed cycloheximide-induced amnesia in mice when given intracerebroventricularly at 10 pg-10 ng.

IT **344-25-2, D-Proline**
RL: RCT (Reactant); RACT (Reactant or reagent)
(peptide coupling of, in preparation of antisenility agent)

RN 344-25-2 HCAPLUS
CN D-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



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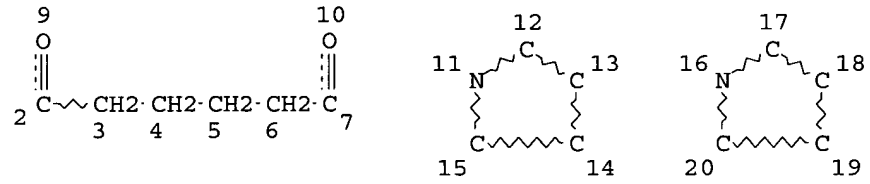
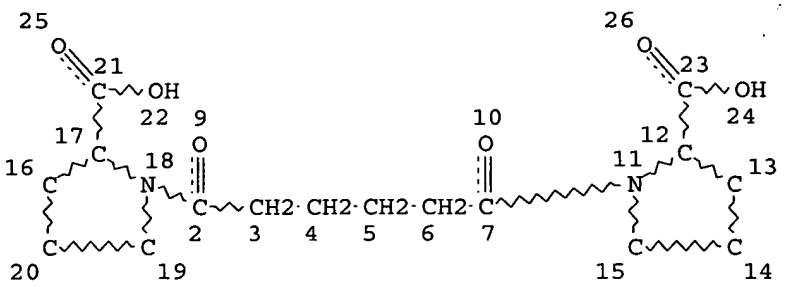
L18 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
L20 538 SEA FILE=REGISTRY SSS FUL L18
L24 305 SEA FILE=HCAPLUS ABB=ON PLU=ON L20
L25 12939 SEA FILE=HCAPLUS ABB=ON PLU=ON SERUM(W)AMYLOID(W)(P OR PROTEIN) OR SAP
L26 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND L25
L27 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE

L28	6	SEA FILE=REGISTRY SUB=L20 SSS FUL L27
L29		SEL PLU=ON L28 1- CHEM : 8 TERMS
L30	9	SEA FILE=HCAPLUS ABB=ON PLU=ON L29
L31	4	SEA FILE=HCAPLUS ABB=ON PLU=ON L30 NOT L26
L35	1	SEA FILE=REGISTRY ABB=ON PLU=ON D-PROLINE/CN
L36	1543	SEA FILE=HCAPLUS ABB=ON PLU=ON L35 OR D(W)PROLINE
L37	3	SEA FILE=HCAPLUS ABB=ON PLU=ON (L36 AND L25) NOT (L26 OR L31)
L38	29	SEA FILE=HCAPLUS ABB=ON PLU=ON (L36 AND (AMYLO? OR ALZHEIM?)) NOT (L26 OR L31 OR L37)
L39	169	SEA FILE=HCAPLUS ABB=ON PLU=ON 6(W)(OXO(2W)HEXANO? OR OXOHEXANO?)
L40	3	SEA FILE=HCAPLUS ABB=ON PLU=ON L39 AND L25
L41	1	SEA FILE=HCAPLUS ABB=ON PLU=ON L40 NOT (L26 OR L31 OR L37 OR L38)

=> d ibib abs hitstr l41 1

L41 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:20511 HCAPLUS
DOCUMENT NUMBER: 134:191514
TITLE: Role of **serum amyloid P** component in bacterial infection: protection of the host or protection of the pathogen
AUTHOR(S): Noursadeghi, Mahdad; Bickerstaff, Maria C. M.; Gallimore, J. Ruth; Herbert, Jeff; Cohen, Jonathan; Pepys, Mark B.
CORPORATE SOURCE: Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine, Royal Free and University College Medical School, London, NW3 2PF, UK
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(26), 14584-14589
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Serum amyloid P** component (**SAP**)

binds to Streptococcus pyogenes, and we show here that it also binds to Neisseria meningitidis, including a lipopolysaccharide (LPS)-neg. mutant, and to rough variants of Escherichia coli. Surprisingly, this binding had a powerful antiopsonic effect both in vitro and in vivo, reducing phagocytosis and killing of bacteria. Furthermore, **SAP** knockout mice survived lethal infection with S. pyogenes and rough E. coli J5, organisms to which **SAP** binds. The susceptibility of **SAP** -/- mice was fully restored by injection of isolated human **SAP.** However, **SAP**-/- mice were more susceptible than wild-type animals to lethal infection with E. coli O111:B4, a smooth strain to which **SAP** does not bind, suggesting that **SAP** also has some host defense function. Although **SAP** binds to LPS in vitro, **SAP**-/- mice were only marginally more susceptible to lethal LPS challenge, and injection of large amts. of human **SAP** into wild-type mice did not affect sensitivity to LPS, indicating that **SAP** is not a significant modulator of LPS toxicity in vivo. In contrast, the binding of **SAP** to pathogenic bacteria enabled them to evade neutrophil phagocytosis and display enhanced virulence. Abrogation of this mol. camouflage is thus potentially a novel therapeutic approach, and we show here that administration to wild-type mice of (R)-1-[6-(R)-2-carboxy-pyrrolidin-1-yl]-**6-oxo-hexanoyl**] pyrrolidine-2-carboxylic acid, a drug that inhibits **SAP** binding, significantly prolonged survival during lethal infection with E. coli J5.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> => d stat que
L42 60 SEA 6(W)(OXO(2W) HEXANO? OR OXOHEXANO?)
L43 15 SEA L42 AND (SAP OR AMYLO?)
L44 10 DUP REMOV L43 (5 DUPLICATES REMOVED)

=> d ibib abs l44 1-10

L44 ANSWER 1 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2004144626 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15036205
TITLE: **Amyloidosis**: a clinico-pathophysiological synopsis.
AUTHOR: Hirschfield Gideon M
CORPORATE SOURCE: NHS National Amyloidosis Centre, Royal Free Hospital, London, UK.. g.hirschfield@rfc.ucl.ac.uk
SOURCE: Seminars in cell & developmental biology, (2004 Feb) 15 (1) 39-44. Ref: 32
Journal code: 9607332. ISSN: 1084-9521.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20040324
Last Updated on STN: 20041027
Entered Medline: 20041026

AB **Amyloidosis** encompasses a spectrum of diseases in which there is disordered folding of certain proteins that leads to them being deposited as insoluble fibrils in the extracellular space. The result of this

process is impaired tissue structure and function. **Amyloidosis** may be acquired or hereditary and local or systemic, and is defined according to the identity of the fibril precursor protein. Over 20 unrelated proteins can form **amyloid** fibrils in vivo, which all share a lamellar cross-beta-sheet structure composed of non-covalently associated protein or peptide subunits. Glycosaminoglycans and the pentraxin protein, serum **amyloid** P component, are universal non-fibrillar constituents of **amyloid** deposits that are believed to play a role in fibrillogenesis and fibril persistence. Greater understanding of the processes underlying **amyloidogenesis**, at all levels from cellular to clinical, has led to improvements in diagnosis, monitoring and treatment of this group of diseases, as well as pointing to possible future therapies.

L44 ANSWER 2 OF 10 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003426917 EMBASE
TITLE: **Amyloidosis**: New strategies for treatment.
AUTHOR: Hirschfield G.M.; Hawkins P.N.
CORPORATE SOURCE: G.M. Hirschfield, Ctr. Amyloidosis/Acute Phase P., NHS National Amyloidosis Centre, Roy. Free/Univ. Coll. Medical School, Rowland Hill Street, London, NW3 2PF, United Kingdom. g.hirschfield@rfc.ucl.ac.uk
SOURCE: International Journal of Biochemistry and Cell Biology, (2003) Vol. 35, No. 12, pp. 1608-1613.
Refs: 19
ISSN: 1357-2725 CODEN: IJBBFU
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20031106
Last Updated on STN: 20031106

AB **Amyloidosis** is a disorder of protein folding in which normally soluble proteins are deposited extracellularly as insoluble fibrils, impairing tissue structure and function. Over 20 unrelated proteins form **amyloid** fibrils in vivo, with fibrils sharing a lamellar cross-β sheet structure, composed of non-covalently associated protein or peptide subunits. **Amyloidosis** may be acquired or hereditary and local or systemic, and is defined according to the precursor protein. Of note, local **amyloid** deposition occurs in Alzheimer's disease (AD) and maturity onset diabetes but their precise role in the pathogenesis of these diseases remains uncertain. Glycosaminoglycans (GAG) and the pentraxin protein, serum **amyloid** P (**SAP**) component, are universal non-fibrillar constituents of **amyloid** deposits that contribute to fibrillogenesis. We review potential therapies for **amyloidosis**, which include measures to reduce the production of **amyloidogenic** precursor proteins, interference with fibrillogenesis, and enhancement of **amyloid** clearance, either by active or passive immunisation or by destabilising deposits through removal of serum **amyloid** P component. .COPYRGT. 2003 Elsevier Ltd. All rights reserved.

L44 ANSWER 3 OF 10 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003143916 EMBASE
TITLE: Pharmacotherapy for Alzheimer's disease: 2002.
AUTHOR: Knopman D.
CORPORATE SOURCE: Dr. D. Knopman, Department of Neurology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, United States. knopman@mayo.edu
SOURCE: Clinical Neuropharmacology, (2003) Vol. 26, No. 2, pp. 93-101.
Refs: 83
ISSN: 0362-5664 CODEN: CLNEDB
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030417
Last Updated on STN: 20030417

AB The intensity of interest in therapy for Alzheimer's disease (AD) has accelerated with each passing year. The nature of the effects of cholinesterase inhibitors has been refined with the publication of several studies that have examined long-term therapy as well as different aspects of the symptomatology of AD. Breakthroughs in the basic science of AD has led to new insights into potential therapeutic strategies targeted at the secretases involved in the metabolism of the Alzheimer precursor protein. An immunization approach in which the **amyloid**-β protein itself was used as the immunizing agent was discontinued after unexpected toxicity occurred. Other areas of investigation with disappointing results such as estrogen replacement therapy and antiinflammatory approaches are discussed. Several other potential therapeutic agents are also reviewed.

L44 ANSWER 4 OF 10 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003091193 EMBASE
TITLE: **Amyloid** inhibitors and Alzheimer's disease.
AUTHOR: Xia W.
CORPORATE SOURCE: W. Xia, Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, 77 Ave. Louis Pasteur, Boston, MA 02115, United States. wxia@rics.bwh.harvard.edu
SOURCE: Current Opinion in Investigational Drugs, (1 Jan 2003) Vol. 4, No. 1, pp. 55-59.
Refs: 53
ISSN: 1472-4472 CODEN: CIDREE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
030 Pharmacology
038 Adverse Reactions Titles
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030313
Last Updated on STN: 20030313

AB Neuritic plaques composed of **amyloid** β-protein (Aβ)

are an early and invariant neuropathological feature of Alzheimer's disease (AD). The current preclinical search for drugs is mainly focused on decreasing Aβ production by inhibiting β- or γ-secretase, blocking the formation of these plaques by preventing Aβ protofibril and fibril formation, and alleviating the toxic effects of neuritic plaque deposition. Increasing numbers of drugs currently used as therapies for other diseases are now entering clinical trials for AD, but the molecular targets of these drugs and their relevance to Aβ toxicity needs to be thoroughly addressed. This knowledge will allow us to fully understand the Aβ-related pathways in AD pathogenesis and explore novel therapeutic interventions.

L44 ANSWER 5 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2002496863 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12357871
TITLE: [Novel therapeutic approach to **amyloidosis**: no implications as yet for patients with Alzheimer's disease]. Nieuwe therapeutische benadering van **amyloidose**: vooralsnog geen implicaties voor patienten met de ziekte van Alzheimer.
AUTHOR: Lemstra A W; Eikelenboom P; Meijer E W; van Gool W A
CORPORATE SOURCE: Academisch Medisch Centrum/Universiteit van Amsterdam, afd. Neurologie, Postbus 22.700, 1100 DE Amsterdam.. a.w.lemstra@amc.uva.nl
SOURCE: Nederlands tijdschrift voor geneeskunde, (2002 Sep 14) 146 (37) 1720-3.
Journal code: 0400770. ISSN: 0028-2162.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Dutch
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021003
Last Updated on STN: 20021218
Entered Medline: 20021213
AB Many disorders, such as Alzheimer's disease and diabetes, are characterised by the misfolding and aggregation of proteins. Pepys et al. described a new approach of destabilizing these aggregates by removing an associated protein, serum **amyloid** P. This offers opportunities for treating **amyloidosis** and possibly other protein folding diseases. Understanding the mechanism of this unique disease process and the different elements involved is necessary for future drug development.

L44 ANSWER 6 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 1
ACCESSION NUMBER: 2002:430106 BIOSIS
DOCUMENT NUMBER: PREV200200430106
TITLE: Targeted pharmacological depletion of serum **amyloid** P component for treatment of human **amyloidosis.**
AUTHOR(S): Pepys, M. B. [Reprint author]; Herbert, J.; Hutchinson, W. L.; Tennent, G. A.; Lachmann, H. J.; Gallimore, J. R.; Lovat, L. B.; Bartfai, T.; Alanine, A.; Hertel, C.; Hoffmann, T.; Jakob-Roetne, R.; Norcross, R. D.; Kemp, J. A.; Yamamura, K.; Suzuki, M.; Taylor, G. W.; Murray, S.; Thompson, D.; Purvis, A.; Kolstoe, S.; Wood, S. P.; Hawkins, P. N.
CORPORATE SOURCE: Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine, Medical School, Royal Free and University College, London, NW3 2PF, UK
m.pepys@rfc.ucl.ac.uk

SOURCE: Nature (London), (16 May, 2002) Vol. 417, No. 6886, pp. 254-259. print.
CODEN: NATUAS. ISSN: 0028-0836.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Aug 2002
Last Updated on STN: 14 Aug 2002

AB The normal plasma protein serum **amyloid** P component (**SAP**) binds to fibrils in all types of **amyloid** deposits, and contributes to the pathogenesis of **amyloidosis.** In order to intervene in this process we have developed a drug, R-1-(6-(R-2-carboxy-pyrrolidin-1-yl)-**6-oxo-hexanoyl**)pyrrolidine-2-carboxylic acid, that is a competitive inhibitor of **SAP** binding to **amyloid** fibrils. This palindromic compound also crosslinks and dimerizes **SAP** molecules, leading to their very rapid clearance by the liver, and thus produces a marked depletion of circulating human **SAP.** This mechanism of drug action potently removes **SAP** from human **amyloid** deposits in the tissues and may provide a new therapeutic approach to both systemic **amyloidosis** and diseases associated with local **amyloid**, including Alzheimer's disease and type 2 diabetes.

L44 ANSWER 7 OF 10 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003099470 EMBASE
TITLE: Small is beautiful again!.
SOURCE: Pharmaceutical News, (2002) Vol. 9, No. 4, pp. 232-233.
Refs: 18
ISSN: 1071-894X CODEN: PHNEEP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
050 Epilepsy
LANGUAGE: English
ENTRY DATE: Entered STN: 20030325
Last Updated on STN: 20030325
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L44 ANSWER 8 OF 10 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002225318 EMBASE
TITLE: [New therapeutic approach in Alzheimer's dementia].
NEUER THERAPIEANSATZ BEI ALZHEIMER-DEMENZ.
SOURCE: Deutsche Apotheker Zeitung, (13 Jun 2002) Vol. 142, No. 24, pp. 41-42.
Refs: 1
ISSN: 0011-9857 CODEN: DAZEA2
COUNTRY: Germany
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: German
ENTRY DATE: Entered STN: 20020711
Last Updated on STN: 20020711
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L44 ANSWER 9 OF 10 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2002245518 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11984001
TITLE: Influenza virus infection is not affected by serum **amyloid** P component.
AUTHOR: Herbert Jeff; Hutchinson Winston L; Carr Jackie; Ives Jane; Jakob-Roetne Roland; Yamamura Ken-Ichi; Suzuki Misao; Pepys Mark B
CORPORATE SOURCE: Department of Medicine, Royal Free and University College Medical School, London, UK.
SOURCE: Molecular medicine (Cambridge, Mass.), (2002 Jan) 8 (1) 9-15.
Journal code: 9501023. ISSN: 1076-1551.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020502
Last Updated on STN: 20020615
Entered Medline: 20020614

AB BACKGROUND: Binding of serum **amyloid** P component (**SAP**) to its ligands, including bacteria, chromatin and **amyloid** fibrils, protects them from degradation, is anti-opsonic and anti-immunogenic. **SAP** thereby enhances the virulence of pathogenic bacteria to which it binds. However **SAP** also contributes to host resistance against bacteria to which it does not bind. Human **SAP** has been reported to bind to the influenza virus and inhibit viral invasion of cells in tissue culture. We therefore investigated a possible role of **SAP** in either host resistance or viral virulence during influenza infection in vivo. MATERIALS AND METHODS: The clinical course of mouse adapted influenza virus infection, the host antibody response, and viral replication, were compared in wild type mice, mice with targeted deletion of the **SAP** gene, and mice transgenic for human **SAP.** The effects of reconstitution of **SAP** deficient mice with pure human **SAP**, and of a drug that specifically blocks **SAP** binding in vivo, were also studied. Binding of mouse and human **SAP** to immobilized influenza virus was compared. RESULTS: The presence, absence, or availability for binding of **SAP** in vivo had no significant or consistent effect on the course or outcome of influenza infection, or on either viral replication or the anti-viral antibody response. Mouse **SAP** bound much less avidly than human **SAP** to influenza virus. CONCLUSIONS: In marked contrast to the dramatic effects of **SAP** deficiency on host resistance to different bacterial infections, mouse **SAP** apparently plays no significant role during infection of mice with influenza virus. Human **SAP** binds much more avidly than mouse **SAP** to the virus, but also had no effect on any of the parameters measured and is therefore unlikely to be involved in human influenza infection.

L44 ANSWER 10 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 3
ACCESSION NUMBER: 2001:84144 BIOSIS
DOCUMENT NUMBER: PREV200100084144
TITLE: Role of serum **amyloid** P component in bacterial infection: Protection of the host or protection of the pathogen.
AUTHOR(S): Noursadeghi, Mahdad; Bickerstaff, Maria C. M.; Gallimore, J. Ruth; Herbert, Jeff; Cohen, Jonathan; Pepys, Mark B. [Reprint author]

CORPORATE SOURCE: Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine, Royal Free and University College Medical School, Rowland Hill Street, London, NW3 2PF, UK
m.pepys@rfc.ucl.ac.uk
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (December 19, 2000) Vol. 97, No. 26, pp. 14584-14589. print.
CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2001
Last Updated on STN: 12 Feb 2002

AB Serum **amyloid** P component (**SAP**) binds to Streptococcus pyogenes, and we show here that it also binds to Neisseria meningitidis, including a lipopolysaccharicle (LPS)-negative mutant, and to rough variants of Escherichia coli. Surprisingly, this binding had a powerful antiopsonic effect both in vitro and in vivo, reducing phagocytosis and killing of bacteria. Furthermore, **SAP** knockout mice survived lethal infection with S. pyogenes and rough E. coli J5, organisms to which **SAP** binds. The susceptibility of **SAP**-/- mice was fully restored by injection of isolated human **SAP.** However, **SAP**-/- mice were more susceptible than wild-type animals to lethal infection with E. coli O111:B4, a smooth strain to which **SAP** does not bind, suggesting that **SAP** also has some host defense function. Although **SAP** binds to LPS in vitro, **SAP**-/- mice were only marginally more susceptible to lethal LPS challenge, and injection of large amounts of human **SAP** into wild-type mice did not affect sensitivity to LPS, indicating that **SAP** is not a significant modulator of LPS toxicity in vivo. In contrast, the binding of **SAP** to pathogenic bacteria enabled them to evade neutrophil phagocytosis and display enhanced virulence. Abrogation of this molecular camouflage is thus potentially a novel therapeutic approach, and we show here that administration to wild-type mice of (R)-1-(6-(R)-2-carboxy-pyrrolidin-1-yl)-**6-oxo-hexanoyl**)pyrrolidine-2-carboxylic acid, a drug that inhibits **SAP** binding, significantly prolonged survival during lethal infection with E. coli J5.

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=> => d stat que
L42          60 SEA 6(W)(OXO(2W) HEXANO? OR OXOHEXANO?)
L43          15 SEA L42 AND (SAP OR AMYLO?)
L44          10 DUP REMOV L43 (5 DUPLICATES REMOVED)
L45          10 SEA L42 AND ALZHEIM?
L46           8 DUP REM L45 (2 DUPLICATES REMOVED)
L47           1 SEA L46 NOT L44

=> d ibib abs l47 1

L47  ANSWER 1 OF 1  EMBASE  COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:   2002461301  EMBASE
TITLE:              Stress proteins and glial functions: Possible therapeutic
                    targets for neurodegenerative disorders.
AUTHOR:             Kimura M.; Kitamura Y.; Nomura Y.
CORPORATE SOURCE:   Y. Nomura, Department of Pharmacology, Grad. Sch. of
                    Pharmaceut. Sciences, Hokkaido University, Sapporo
                    060-0812, Japan. nomura@pharm.hokudai.ac.jp
SOURCE:             Pharmacology and Therapeutics, (1 Jan 2003) Vol. 97, No. 1,
```

pp. 35-53.
Refs: 201
ISSN: 0163-7258 CODEN: PHTHDT
PUBLISHER IDENT.: S 0163-7258(02)00301-7
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030109
Last Updated on STN: 20030109

AB Recent findings suggest that unfolded or misfolded proteins participate in the pathology of several neurodegenerative disorders, such as **Alzheimer**'s disease and Parkinson's disease. Usually, several stress proteins and glial cells act as intracellular molecular chaperones and show chaperoning neuronal function, respectively. In the brains of patients with neurodegenerative disorders, however, stress proteins are expressed and frequently associated with protein aggregates, and glial cells are activated around degenerative regions. In addition, several stress proteins and glial cells may also regulate neuronal cell death and loss. Therefore, some types of stress proteins and glial cells are considered to be neuroprotective targets. We summarize the current findings regarding the neuroprotective effects of stress proteins and glial cells, and discuss the possibility of using this knowledge to develop new therapeutic strategies to treat neurodegeneration. .COPYRGT. 2002 Elsevier Science Inc. All rights reserved.

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File  35:Dissertation Abs Online 1861-2005/Aug
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         (c) 2005 Inst for Sci Info
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Set     Items   Description
S1        172   (6(W)(OXO(2W)HEXANO? OR OXOHEXANO?))
S2     307545   (SAP OR AMYLOD? OR ALZHEIM?)
S3         26   S1 AND S2
S4         16   RD (unique items)
?
? T S4/3 AB/1-16

 4/AB/1     (Item 1 from file: 24)
DIALOG(R)File  24:CSA Life Sciences Abstracts
(c) 2005 CSA. All rts. reserv.

0002317406       IP ACCESSION NO: 5375310
Targeted pharmacological depletion of serum amyloid P component for
treatment of human amyloidosis

Pepys, MB;  Herbert, J;  Hutchinson, WL;  Tennent, GA;  Lachmann, HJ;
Gallimore, JR;  Lovat, LB;  Bartfai, T;  Alanine, A;  Hertel, C;  Hoffmann,
T;  Jakob-Roetne, R;  Norcross, RD;  Hawkins, PN;  et al.
Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine,
Royal Free and University College Medical School, London NW3 2PF, UK,
[mailto:m.pepys@rfc.ucl.ac.uk]

Nature, v 417, n 6886, p 254-259, May 16, 2002
PUBLICATION DATE: 2002

PUBLISHER: Macmillan Publishers Ltd.

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 0028-0836
FILE SEGMENT: CSA Neurosciences Abstracts
```

ABSTRACT:
The normal plasma protein serum amyloid P component (**SAP**) binds to fibrils in all types of amyloid deposits, and contributes to the pathogenesis of amyloidosis. In order to intervene in this process we have developed a drug, R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-**6-oxo-hexanoyl**]pyrrolidine-2- carboxyli c acid, that is a competitive inhibitor of **SAP** binding to amyloid fibrils. This palindromic compound also crosslinks and dimerizes **SAP** molecules, leading to their very rapid clearance by the liver, and thus produces a marked depletion of circulating human **SAP**. This mechanism of drug action potently removes **SAP** from human amyloid deposits in the tissues and may provide a new therapeutic approach to both systemic amyloidosis and diseases associated with local amyloid, including **Alzheimer**'s disease and type 2 diabetes.
Abstract

4/AB/2 (Item 2 from file: 24)
DIALOG(R)File 24:CSA Life Sciences Abstracts
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0002165759 IP ACCESSION NO: 4800986
Role of serum amyloid P component in bacterial infection: Protection of the host or protection of the pathogen

Noursadeghi, M; Bickerstaff, MCM; Gallimore, JR; Herbert, J; Cohen, J; Pepys, MB
Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine, Royal Free and University College Medical School, London NW3 2PF, United Kingdom, [mailto:m.pepys@rfc.ucl.ac.uk]

Proceedings of the National Academy of Sciences, USA, v 97, n 26, p 14584-14589, December 19, 2000
PUBLICATION DATE: 2000

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 0027-8424
FILE SEGMENT: Bacteriology Abstracts (Microbiology B)
ABSTRACT:
Serum amyloid P component (**SAP**) binds to Streptococcus pyogenes, and we show here that it also binds to Neisseria meningitidis, including a lipopolysaccharide (LPS)-negative mutant, and to rough variants of Escherichia coli. Surprisingly, this binding had a powerful antiopsonic effect both in vitro and in vivo, reducing phagocytosis and killing of bacteria. Furthermore, **SAP** knockout mice survived lethal infection with S. pyogenes and rough E. coli J5, organisms to which **SAP** binds. The susceptibility of **SAP** super(-/-) mice was fully restored by injection of isolated human **SAP**. However, **SAP** super(-/-) mice were more susceptible than wild-type animals to lethal infection with E. coli O111:B4, a smooth strain to which **SAP** does not bind, suggesting that **SAP** also has some host defense function. Although **SAP** binds to LPS in vitro, **SAP** super(-/-) mice were only marginally more susceptible to lethal LPS challenge, and injection of large amounts of human **SAP** into wild-type mice did not affect sensitivity to LPS, indicating that **SAP** is not a significant modulator of LPS toxicity in vivo. In contrast, the binding of **SAP** to pathogenic bacteria enabled them to evade neutrophil phagocytosis and display enhanced virulence.

Abrogation of this molecular camouflage is thus potentially a novel therapeutic approach, and we show here that administration to wild-type mice of (R)-1-[6-(R)-2-carboxy-pyrrolidin- 1-yl]-**6-oxo-hexanoyl**]pyrrolidine-2- carboxylic acid, a drug that inhibits **SAP** binding, significantly prolonged survival during lethal infection with E. coli J5.
Abstract

4/AB/3 (Item 1 from file: 35)
DIALOG(R)File 35:Dissertation Abs Online
(c) 2005 ProQuest Info&Learning. All rts. reserv.

01943359 AADAAIC813045
Amyloid recognition by serum amyloid P component
Author: Purvis, Alan
Degree: Ph.D.
Year: 2002
Corporate Source/Institution: University of Southampton (United Kingdom) (5036)
Source: VOLUME 64/03-C OF DISSERTATION ABSTRACTS INTERNATIONAL. PAGE 679

The X-ray crystal structures of serum amyloid P component (**SAP**) with bound (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-**6-oxo-hexanoyl**]-pyrrolidine-2-carboxylic acid (Ro 63-8695) and related components have been solved to elucidate the molecular basis of the action of Ro 63-8695, a potential amyloid mobilizing drug for treatment of human amyloid disease. The structure of **SAP** in the presence of N-acetyl-D-proline has been determined to a resolution of 2.4Å using a previously solved **SAP** structure as the phasing model (unit cell dimensions a = 96.1Å, b = 70.8Å, c = 103.6Å, and β = 96.8°). The carboxyl group of N-acetyl-D-proline is bound in the double calcium-binding site of each subunit, orientating the pyrrolidine ring into the adjacent hydrophobic pocket formed between Leu62, Tyr64, and Tyr74. The structure of **SAP** co-crystallised with Ro 63-8695 has been determined to a resolution of 3.2Å by molecular replacement (unit cell dimensions a = b = 230.9Å and c = 281.4Å). This shows the formation of a ligand-induced decamer, where two **SAP** pentamers are reversibly cross-linked by five Ro 63-8695 molecules. Binding of the Ro 63-8695 molecule head group shows close superposition with the higher resolution N-acetyl-D-proline structure. The alkyl linker adopts a kinked rotamer about carbons 2 and 3 to facilitate binding of the head groups to the two-fold axis related subunits. The best fit of the electron density is found when both peptide bonds preceding the pyrrolidine ring adopt a cis conformation. Nuclear magnetic resonance spectroscopy has estimated this cis-cis isomer to contribute only ∼6% of the Ro 63-8695 population in free solution. **SAP** has also been found to enhance the refolding yield of denatured lactate dehydrogenase and protects against enzyme inactivation during agitation through a calcium independent site.

4/AB/4 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2005 Elsevier Science B.V. All rts. reserv.

12313372 EMBASE No: 2003426917
Amyloidosis: New strategies for treatment
Hirschfield G.M.; Hawkins P.N.
G.M. Hirschfield, Ctr. Amyloidosis/Acute Phase P., NHS National

Amyloidosis Centre, Roy. Free/University Coll. Medical School, Rowland Hill Street, London, NW3 2PF United Kingdom
AUTHOR EMAIL: g.hirschfield@rfc.ucl.ac.uk
International Journal of Biochemistry and Cell Biology (INT. J. BIOCHEM. CELL BIOL.) (United Kingdom) 2003, 35/12 (1608-1613)
CODEN: IJBBF ISSN: 1357-2725
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 19

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited extracellularly as insoluble fibrils, impairing tissue structure and function. Over 20 unrelated proteins form amyloid fibrils in vivo, with fibrils sharing a lamellar cross-beta sheet structure, composed of non-covalently associated protein or peptide subunits. Amyloidosis may be acquired or hereditary and local or systemic, and is defined according to the precursor protein. Of note, local amyloid deposition occurs in **Alzheimer**'s disease (AD) and maturity onset diabetes but their precise role in the pathogenesis of these diseases remains uncertain. Glycosaminoglycans (GAG) and the pentraxin protein, serum amyloid P (**SAP**) component, are universal non-fibrillar constituents of amyloid deposits that contribute to fibrillogenesis. We review potential therapies for amyloidosis, which include measures to reduce the production of amyloidogenic precursor proteins, interference with fibrillogenesis, and enhancement of amyloid clearance, either by active or passive immunisation or by destabilising deposits through removal of serum amyloid P component. (c) 2003 Elsevier Ltd. All rights reserved.

4/AB/5 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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12031951 EMBASE No: 2003143916
Pharmacotherapy for **Alzheimer**'s disease: 2002
Knopman D.
Dr. D. Knopman, Department of Neurology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905 United States
AUTHOR EMAIL: knopman@mayo.edu
Clinical Neuropharmacology (CLIN. NEUROPHARMACOL.) (United States) 2003, 26/2 (93-101)
CODEN: CLNED ISSN: 0362-5664
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 83

The intensity of interest in therapy for **Alzheimer**'s disease (AD) has accelerated with each passing year. The nature of the effects of cholinesterase inhibitors has been refined with the publication of several studies that have examined long-term therapy as well as different aspects of the symptomatology of AD. Breakthroughs in the basic science of AD has led to new insights into potential therapeutic strategies targeted at the secretases involved in the metabolism of the **Alzheimer** precursor protein. An immunization approach in which the amyloid-beta protein itself was used as the immunizing agent was discontinued after unexpected toxicity occurred. Other areas of investigation with disappointing results such as estrogen replacement therapy and antiinflammatory approaches are discussed. Several other potential therapeutic agents are also reviewed.

4/AB/6 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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11988957 EMBASE No: 2003099470
Small is beautiful again!
Pharmaceutical News (PHARM. NEWS) (United Kingdom) 2002, 9/4 (232-233)
CODEN: PHNEE ISSN: 1071-894X
DOCUMENT TYPE: Journal ; Short Survey
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 18

4/AB/7 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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11980612 EMBASE No: 2003091193
Amyloid inhibitors and **Alzheimer**'s disease
Xia W.
W. Xia, Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, 77 Ave. Louis Pasteur, Boston, MA 02115 United States
AUTHOR EMAIL: wxia@rics.bwh.harvard.edu
Current Opinion in Investigational Drugs (CURR. OPIN. INVEST. DRUGS) (United Kingdom) 01 JAN 2003, 4/1 (55-59)
CODEN: CIDRE ISSN: 1472-4472
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 53

Neuritic plaques composed of amyloid beta-protein (Abeta) are an early and invariant neuropathological feature of **Alzheimer**'s disease (AD). The current preclinical search for drugs is mainly focused on decreasing Abeta production by inhibiting beta- or gamma-secretase, blocking the formation of these plaques by preventing Abeta protofibril and fibril formation, and alleviating the toxic effects of neuritic plaque deposition. Increasing numbers of drugs currently used as therapies for other diseases are now entering clinical trials for AD, but the molecular targets of these drugs and their relevance to Abeta toxicity needs to be thoroughly addressed. This knowledge will allow us to fully understand the Abeta-related pathways in AD pathogenesis and explore novel therapeutic interventions.

4/AB/8 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2005 Elsevier Science B.V. All rts. reserv.

11888745 EMBASE No: 2002461301
Stress proteins and glial functions: Possible therapeutic targets for neurodegenerative disorders
Kimura M.; Kitamura Y.; Nomura Y.
Y. Nomura, Department of Pharmacology, Grad. Sch. of Pharmaceut. Sciences, Hokkaido University, Sapporo 060-0812 Japan
AUTHOR EMAIL: nomura@pharm.hokudai.ac.jp
Pharmacology and Therapeutics (PHARMACOL. THER.) (United States) 01 JAN 2003, 97/1 (35-53)
CODEN: PHTHD ISSN: 0163-7258

PUBLISHER ITEM IDENTIFIER: S0163725802003017
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 201

Recent findings suggest that unfolded or misfolded proteins participate in the pathology of several neurodegenerative disorders, such as **Alzheimer**'s disease and Parkinson's disease. Usually, several stress proteins and glial cells act as intracellular molecular chaperones and show chaperoning neuronal function, respectively. In the brains of patients with neurodegenerative disorders, however, stress proteins are expressed and frequently associated with protein aggregates, and glial cells are activated around degenerative regions. In addition, several stress proteins and glial cells may also regulate neuronal cell death and loss. Therefore, some types of stress proteins and glial cells are considered to be neuroprotective targets. We summarize the current findings regarding the neuroprotective effects of stress proteins and glial cells, and discuss the possibility of using this knowledge to develop new therapeutic strategies to treat neurodegeneration. (c) 2002 Elsevier Science Inc. All rights reserved.

4/AB/9 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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11653374 EMBASE No: 2002225318
New therapeutic approach in **Alzheimer**'s dementia
NEUER THERAPIEANSATZ BEI **ALZHEIMER**-DEMENZ
Deutsche Apotheker Zeitung (DTSCH. APOTH. ZTG.) (Germany) 13 JUN 2002
, 142/24 (41-42)
CODEN: DAZEA ISSN: 0011-9857
DOCUMENT TYPE: Journal ; Note
LANGUAGE: GERMAN
NUMBER OF REFERENCES: 1

4/AB/10 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2005 Elsevier Science B.V. All rts. reserv.

11585065 EMBASE No: 2002156663
Influenza virus infection is not affected by serum amyloid P component
Herbert J.; Hutchinson W.L.; Carr J.; Ives J.; Jakob-Roetne R.; Yamamura
K.-I.; Suzuki M.; Pepys M.B.
M.B. Pepys, Ctr. Amyloidosis/A. Phase Proteins, Department of Medicine, Royal Free and University Coll. Med. Sch., Rowland Hill Street, London NW3 2PF United Kingdom
AUTHOR EMAIL: m.pepys@rfc.ucl.ac.uk
Molecular Medicine (MOL. MED.) (United States) 2002, 8/1 (9-15)
CODEN: MOMEE ISSN: 1076-1551
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 30

Background: Binding of serum amyloid P component (**SAP**) to its ligands, including bacteria, chromatin and amyloid fibrils, protects them from degradation, is anti-opsonic and anti-immunogenic. **SAP** thereby enhances the virulence of pathogenic bacteria to which it binds. However **SAP** also contributes to host resistance against bacteria to which it

does not bind. Human **SAP** has been reported to bind to the influenza virus and inhibit viral invasion of cells in tissue culture. We therefore investigated a possible role of **SAP** in either host resistance or viral virulence during influenza infection in vivo. Materials and Methods: The clinical course of mouse adapted influenza virus infection, the host antibody response, and viral replication, were compared in wild type mice, mice with targeted deletion of the **SAP** gene, and mice transgenic for human **SAP**. The effects of reconstitution of **SAP** deficient mice with pure human **SAP**, and of a drug that specifically blocks **SAP** binding in vivo, were also studied. Binding of mouse and human **SAP** to immobilized influenza virus was compared. Results: The presence, absence, or availability for binding of **SAP** in vivo had no significant or consistent effect on the course or outcome of influenza infection, or on either viral replication or the anti-viral antibody response. Mouse **SAP** bound much less avidly than human **SAP** to influenza virus. Conclusions: In marked contrast to the dramatic effects of **SAP** deficiency on host resistance to different bacterial infections, mouse **SAP** apparently plays no significant role during infection of mice with influenza virus. Human **SAP** binds much more avidly than mouse **SAP** to the virus, but also had no effect on any of the parameters measured and is therefore unlikely to be involved in human influenza infection.

4/AB/11 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI
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016724198
WPI Acc No: 2005-048473/200505
XRAM Acc No: C05-016553
Use of an agent inhibiting serum amyloid ligand binding activity or depleting serum amyloid from the plasma, in the treatment prevention of osteoarthritis
Patent Assignee: PENTRAXIN THERAPEUTICS LTD (PENT-N)
Inventor: HAWKINS P N; PEPYS M B
Number of Countries: 108 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 2004108131	A1	20041216	WO 2004GB2445	A	20040610	200505	B

Priority Applications (No Type Date): GB 200313386 A 20030610
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 2004108131	A1	E	51	A61K-031/401	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
Designated States (Regional): AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

Abstract (Basic): WO 2004108131 A1
Abstract (Basic):
NOVELTY - In the production of medicament for treatment or prevention of osteoarthritis, an agent capable of inhibiting serum amyloid P (**SAP**) ligand binding activity or depleting **SAP** from the plasma is used.

ACTIVITY - Antiarthritic; Osteopathic.
MECHANISM OF ACTION - Serum amyloid P inhibitor
USE - For treatment or prevention of osteoarthritis (claimed)
ADVANTAGE - Use of the agent causes dramatic effect in relieving symptoms of the disease.
pp; 51 DwgNo 0/5

4/AB/12 (Item 2 from file: 351)
DIALOG(R)File 351:Derwent WPI
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016376262
WPI Acc No: 2004-534169/200451
Related WPI Acc No: 2004-534013
XRAM Acc No: C04-196533
Promoting wound healing in mammal, involves supplying composition operable to deplete serum amyloid P (**SAP**) or suppress **SAP** activity, to mammal having wound containing **SAP**, thus suppressing monocyte differentiation into fibrocytes
Patent Assignee: UNIV RICE WILLIAM MARSH (UYRI-N)
Inventor: GOMER R; PILLING D
Number of Countries: 107 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200459318	A2	20040715	WO 2003US41183	A	20031222	200451	B
AU 2003299873	A1	20040722	AU 2003299873	A	20031222	200476	

Priority Applications (No Type Date): US 2003525175 P 20031126; US 2002436027 P 20021223; US 2002436046 P 20021223; US 2003515776 P 20031030 ; US 2003519467 P 20031112
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200459318	A2	E	65	G01N-033/50	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
Designated States (Regional): AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

AU 2003299873	A1	G01N-033/50	Based on patent WO 200459318

Abstract (Basic): WO 200459318 A2
Abstract (Basic):
NOVELTY - Promoting (M1) wound healing in mammal, involves supplying a composition operable to deplete serum amyloid P (**SAP**) or suppress **SAP** activity, to mammal having a wound containing **SAP**, where the composition is supplied in an amount and for a time period sufficient to suppress the ability of the **SAP** to suppress monocyte differentiation into fibrocytes.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) wound dressing (I) comprising agarose that promotes wound healing in mammal; and
(2) detecting (M2) the ability of an agent to promote fibrocyte formation, involves providing a sample containing monocytes with an agent at a known concentration to form a test mixture, incubating the test mixture for 48-72 hours and examining the test mixture for the

presence of fibrocytes, where the presence of abnormally high number of fibrocytes indicates that the agent at the known concentration is able to promote monocyte differentiation into fibrocytes.

ACTIVITY - Vulnerary; Antidiabetic; Antiulcer.

MECHANISM OF ACTION - Suppressor of **SAP** activity; Suppressor of differentiation of monocyte (claimed); Angiogenesis stimulator.

To test the effects of calcium/agarose bandage on wound healing, the following test was done. About 4 cm wounds through the entire thickness of skin were made on the back of three anesthetized rats. One rat was treated only with 4X4 gauze bandage (Topper 4X4 sponge gauze, Johnson and Johnson, Skillman, NJ) lightly soaked with 1 ml saline solution (0.9 sodium chloride weight/volume% in water). The second rat was treated with a similar bandage, with the first layer lightly soaked (1 ml) with saline/5 mM CaCl2. The third rat was treated with agarose/CaCl2 bandage. Each rat was separately anesthetized, photographed and bandaged to minimize the differences in time between anesthetizing, wounding and bandaging. After 24 hours, the rats were lightly anesthetized and weighed, then the bandages were removed and the wounds were photographed. New bandages of the same initial composition were then reapplied to each of the rats. After another 24 hours, the above process was repeated. The results showed that the rat treated with agarose/CaCl2 bandage showed considerably more rapid wound healing than either of the other two rats.

USE - (M1) is useful for promoting wound healing in mammal e.g., human, or for increasing number of fibrocytes present in sample (claimed). (M1) is useful for tissue engineering, for inducing angiogenesis in regions that are in need of new vasculature, for cosmetic surgery applications, or for treating patients suffering from lacerations, diabetic complications e.g., ulcers, pressure ulcers or open fractures.

DESCRIPTION OF DRAWING(S) - The figure is a graph that shows the effect of on fibrocyte differentiation of depleting serum amyloid P from plasma with BioGel agarose beads.

pp; 65 DwgNo 5A/9

4/AB/13 (Item 3 from file: 351)
DIALOG(R)File 351:Derwent WPI
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016011435
WPI Acc No: 2004-169286/200416
XRAM Acc No: C04-067029
Use of an agent e.g. one glutamate modifying enzyme or a glutamate-pyruvate transaminase for reduction of blood glutamate levels in disease conditions, e.g. **Alzheimer**'s disease
Patent Assignee: YEDA RES & DEV CO LTD (YEDA)
Inventor: TEICHBERG V I
Number of Countries: 106 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200412762	A2	20040212	WO 2003IL634	A	20030731	200416	B
AU 2003247143	A1	20040223	AU 2003247143	A	20030731	200453	
EP 1524989	A2	20050427	EP 2003766600	A	20030731	200529	
			WO 2003IL634	A	20030731		

Priority Applications (No Type Date): US 2002430689 P 20021204; US 2002399708 P 20020801
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes

WO 200412762 A2 E 100 A61K-038/43
Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
AU 2003247143 A1 A61K-038/43 Based on patent WO 200412762
EP 1524989 A2 E A61K-038/43 Based on patent WO 200412762
Designated States (Regional): AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR

Abstract (Basic): WO 200412762 A2
Abstract (Basic):

NOVELTY - Reduction of extracellular brain glutamate levels comprising the administration of an agent (I) capable of reducing blood glutamate levels, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) an article of manufacture comprising packaging material and a pharmaceutical composition having an active ingredient for reducing extracellular brain glutamate levels; and

(2) a method of reducing extracellular brain glutamate levels in a subject comprising obtaining a blood sample, contacting the blood sample with (I) to obtain the glutamate depleted blood cells (A) and introducing (A) in to the subject.

ACTIVITY - Cerebroprotective; Anti HIV; Vasotropic; Tranquilizer; Vulnerary; Antibacterial; Neuroprotective; Hemostatic; Anticonvulsant; Hepatotropic; Ophthalmological; Nootropic.

MECHANISM OF ACTION - Glutamate synthesizing enzyme inhibitor; Glutamate modifier.

(I) were assessed with Adult Sprague Dawley Rat blood sample. The results showed significant increase in blood glutamate upon incubation with 2.5 microm/ml (GPT) and complete reversion on addition of pyruvate at 0 minutes, 15 minutes and 30 minutes and activation of GPT by pyruvate caused decrease in glutamate level and when blood sample was supplemented with oxaloacetate at 0 minutes, 15 minutes and 30 minutes, resulting in more rapid activation of GOT by oxaloacetate and greater decline in glutamate levels GPT/GOT mediated glutamate conversion reached a maximal extent limited by concomitant 2-alpha-ketoglutarate concentration build up during GPT and GOT reverse condition.

USE - (I) is useful for treating brain anoxia, stroke, perinatal brain damage, traumatic brain injury, bacterial meningitis, subarachnoid hemorrhage, epilepsy, acute liver failure, glaucoma, amyotrophic lateral sclerosis, HIV, dementia, hemorrhagic shock, open heart surgery, aneurism, surgery, coronary artery bypass surgery grafting or **Alzheimer**'s disease (claimed).

ADVANTAGE - (I) protects neural tissue from damage induced by glutamate levels.

pp; 100 DwgNo 0/33

4/AB/14 (Item 4 from file: 351)
DIALOG(R)File 351:Derwent WPI
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015535964
WPI Acc No: 2003-598114/200356
XRAM Acc No: C03-162191

New D-proline prodrugs used for treating all forms of central and systemic amyloidosis e.g. **Alzheimer**'s disease, chronic inflammatory disorders and chronic infections

Patent Assignee: HOFFMANN LA ROCHE & CO AG F (HOFF); HUWYLER J (HUWY-I); JAKOB-ROETNE R (JAKO-I); POLI S M (POLI-I); HOFFMANN LA ROCHE INC (HOFF)

Inventor: HUWYLER J; JAKOB-ROETNE R; POLI S M

Number of Countries: 102 Number of Patents: 012

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200351836	A1	20030626	WO 2002EP13827	A	20021206	200356 B
US 20030134891	A1	20030717	US 2002307699	A	20021202	200356
AU 2002361982	A1	20030630	AU 2002361982	A	20021206	200420
EP 1458680	A1	20040922	EP 2002796578	A	20021206	200462
			WO 2002EP13827	A	20021206	
KR 2004063992	A	20040715	KR 2004709036	A	20040611	200473
BR 200214932	A	20041130	BR 200214932	A	20021206	200506
			WO 2002EP13827	A	20021206	
NO 200402979	A	20040713	WO 2002EP13827	A	20021206	200513
			NO 20042979	A	20040713	
HU 200402600	A2	20050329	WO 2002EP13827	A	20021206	200528
			HU 20042600	A	20021206	
JP 2005515211	W	20050526	WO 2002EP13827	A	20021206	200535
			JP 2003552723	A	20021206	
US 6903129	B2	20050607	US 2002307699	A	20021202	200538
TW 225400	B1	20041221	TW 2002135829	A	20021211	200540
CN 1604892	A	20050406	CN 2002824934	A	20021206	200553

Priority Applications (No Type Date): EP 2001129793 A 20011214

Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200351836	A1	E	14	C07D-207/16	
	Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW				
	Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW				
US 20030134891	A1			A61K-031/4025	
AU 2002361982	A1			C07D-207/16	Based on patent WO 200351836
EP 1458680	A1	E		C07D-207/16	Based on patent WO 200351836
	Designated States (Regional): AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR				
KR 2004063992	A			C07D-403/06	
BR 200214932	A			C07D-207/16	Based on patent WO 200351836
NO 200402979	A			C07D-207/16	
HU 200402600	A2			C07D-207/16	Based on patent WO 200351836
JP 2005515211	W		25	C07D-207/16	Based on patent WO 200351836
US 6903129	B2			C07D-267/22	
TW 225400	B1			A61K-031/401	
CN 1604892	A			C07D-207/16	

Abstract (Basic): WO 200351836 A1

Abstract (Basic):

NOVELTY - D-proline prodrugs (I) and (II) are new.

DETAILED DESCRIPTION - D-proline prodrugs of formula (I) and (II) and their salts are new.

R1, R2=lower alkoxy, lower alkenyloxy, benzyloxy, OH,

OCH(CH3)OC(O)-lower alkyl or OCH2C(O)N(R3)(R4); or
R1 + R2=O(CH2)nCH=CH(CH2)nO or O(CH2)mO;
R3, R4=H, lower alkyl, lower alkenyl or cycloalkyl;
n=1-3; and
m=4-8;
provided that only one of R1 or R2 is OH.
ACTIVITY - Nootropic; Neuroprotective; Antidiabetic; Cardiant; Nephrotropic; Antiinflammatory; Antimicrobial; Cytostatic.
A test is described, but no relevant results are given.
MECHANISM OF ACTION - None given.
USE - Used in the treatment of all forms of central and systemic amyloidosis (claimed), particularly **Alzheimer**'s disease, maturity onset diabetes mellitus, amyloidosis due to non-ischemic heart failure, complication of long term hemodialysis in renal failure and monoclonal gammopathies, chronic inflammatory disorders, chronic infections and certain types of cancer, hereditary amyloidosis (e.g. familial amyloid polyneuropathy, scrapie and Kreuzfeld-Jakob disease), and bacterial infections.
ADVANTAGE - (I) And (II) enhance bioavailability and passage through biological barriers, increase the duration of pharmacological effects and site specificity, reduce toxicity and adverse effects and have improved organoleptic properties, stability and solubility. The compounds exhibit low stabilities in plasma.
pp; 14 DwgNo 0/0

4/AB/15 (Item 5 from file: 351)
DIALOG(R)File 351:Derwent WPI
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015187701
WPI Acc No: 2003-248235/200324
XRAM Acc No: C03-064083
New non-proteinaceous agent useful for depletion of an unwanted protein population from plasma, comprises a compound with ligands covalently co-linked to form a complex with proteins
Patent Assignee: UNIV COLLEGE LONDON (UNLO); PENTRAXIN THERAPEUTICS LTD (PENT-N)
Inventor: PEPYS M B
Number of Countries: 101 Number of Patents: 004
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200313508	A1	20030220	WO 2002GB3504	A	20020729	200324	B
EP 1418905	A1	20040519	EP 2002751356	A	20020729	200433	
			WO 2002GB3504	A	20020729		
AU 2002355355	A1	20030224	AU 2002355355	A	20020729	200461	
JP 2005501071	W	20050113	WO 2002GB3504	A	20020729	200506	
			JP 2003518517	A	20020729		

Priority Applications (No Type Date): US 2001985699 A 20011105; GB 200119370 A 20010808
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200313508	A1	E	54	A61K-031/401	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB

GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
EP 1418905 A1 E A61K-031/401 Based on patent WO 200313508
Designated States (Regional): AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
AU 2002355355 A1 A61K-031/401 Based on patent WO 200313508
JP 2005501071 W 85 A61K-031/4025 Based on patent WO 200313508

Abstract (Basic): WO 200313508 A1
Abstract (Basic):

NOVELTY - New agent (A) for depletion of an unwanted protein population from plasma, comprises a compound having ligands covalently co-linked so as to form a complex with proteins.

DETAILED DESCRIPTION - An agent (A) for depletion of an unwanted protein population from plasma, where the agent comprises ligands covalently co-linked so as to form a complex with proteins, where at least 2 of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins, and the agent is a non-proteinaceous agent other than a D-proline of formula (IA) or (IB), is new;

R=a group of formula (i);

R1=H or halo;

X=-(CH2)n , -CH(R2)(CH2)n-, -CH2O(CH2)n-, -CH2NH-, benzyl, C(R2)=CH , -CH2CH(OH)- or thiazol-2,5-diyl;

Y=-S-S-, (CH2)n-, -O-, NH-, -N(R2)-, -CH=CH-, -NHC(O)NH-, N(R2)C(O)N(R2)-, N(CH2C6H3(OCH3)2)-, -N(CH2C6H5)-, N(CH2C6H5)C(O)N(CH2C6H5)-, -N(alkoxyalkyl)-, N(cycloalkylmethyl)-, 2,6-pyridyl, 2,5-furanyl, 2,5-thienyl; 1,2, 1,3- or 1,4-cyclohexyl; 1,2-, 1,4-, 1,5- or 1,6-naphthyl; biphenylene; or 1,2-, 1,3- or 1,4-phenylene, where phenylene are optionally substituted by 1-4 halo, lower alkyl, lower alkoxy, OH, carboxy, -COO-lower alkyl, CN, 5-tetrazol, (2-carboxylic acid pyrrolidin-1-yl)-2-oxo-ethoxy, N-hydroxycarbamimidoyl, 5-oxo(1,2,4)oxadiazolyl, 2-oxo-(1,2,3,5)oxathiadiazolyl, 5-thioxo(1,2,4)oxadiazolyl or 5-tert. butylsulfanyl(1,2,4)oxadiazolyl;

X'=-(CH2)n-, (CH2)nCH(R2)-, -(CH2)nOCH2-, -NHCH2-, benzyl, -CH=C(R2)-, -CH(OH)CH2 or thiazol-2,5-diyl;

R2=lower alkyl, lower alkoxy or benzyl;

n=0-3.

An INDEPENDENT CLAIM is also included for the use of a non proteinaceous agent for the preparation of a composition for depletion of an unwanted protein population from plasma, where the agent (preferably (IA) or (IB)) comprises ligands covalently co-linked so as to form a complex with proteins, where at least 2 of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins.

ACTIVITY - None given.

MECHANISM OF ACTION - Serum Amyloid P Inhibitor.

8 Patients with systemic amyloidosis, 1 with minor localized AL amyloidosis, and 1 who was a carrier of the amyloidogenic Ala60 transthyretin variant were treated with (R)-1-(6-(R)-2-carboxy pyrrolidin-1-yl)-**6-oxo-hexanoyl**)pyrrolidine-2-carboxylic acid (Ia) by intravenous infusion for 48 hours. There was dramatic, rapid and consistent depletion of circulating **SAP** in all subjects.

In a further study, using quantitative whole body scintigraphy with 123I-**SAP** as tracer, each patient received a standard dose of 123I-**SAP** before (Ia) infusion started. Patients were scanned immediately before treatment, then at intervals up to 48 hours. (Ia) caused dramatic clearance of tracer from the plasma. By 6 hours after starting treatment, the blood pool signal virtually disappeared, and

there was accumulation of tracer in the liver. At the same time, there was a marked decrease in the retention of tracer in amyloid deposits elsewhere.

USE - (A) is used for the depletion of an unwanted protein population from plasma (claimed) of humans or animals.

pp; 54 DwgNo 0/8

4/AB/16 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
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0346398 DBR Accession No.: 2004-18690 PATENT
Promoting wound healing in mammal, involves supplying composition operable to deplete serum amyloid P (**SAP**) or suppress **SAP** activity, to mammal having wound containing **SAP**, thus suppressing monocyte differentiation into fibrocytes - deplete serum amyloid-P composition for fibrocyte differentiation suppression and tissue engineering
AUTHOR: GOMER R; PILLING D
PATENT ASSIGNEE: UNIV RICE WILLIAM MARSH 2004
PATENT NUMBER: WO 200459318 PATENT DATE: 20040715 WPI ACCESSION NO.: 2004-534169 (200451)
PRIORITY APPLIC. NO.: US 525175 APPLIC. DATE: 20031126
NATIONAL APPLIC. NO.: WO 2003US41183 APPLIC. DATE: 20031222
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Promoting (M1) wound healing in mammal, involves supplying a composition operable to deplete serum amyloid P (**SAP**) or suppress **SAP** activity, to mammal having a wound containing **SAP**, where the composition is supplied in an amount and for a time period sufficient to suppress the ability of the **SAP** to suppress monocyte differentiation into fibrocytes.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) wound dressing (I) comprising agarose that promotes wound healing in mammal; and (2) detecting (M2) the ability of an agent to promote fibrocyte formation, involves providing a sample containing monocytes with an agent at a known concentration to form a test mixture, incubating the test mixture for 48-72 hours and examining the test mixture for the presence of fibrocytes, where the presence of abnormally high number of fibrocytes indicates that the agent at the known concentration is able to promote monocyte differentiation into fibrocytes. BIOTECHNOLOGY - Preferred Method: (M1) further involves increasing the number of fibrocytes present in the wound, and depleting **SAP** or suppressing **SAP** activity in the wound. The composition consists of R-1-(6-(R-2-carboxy-pyrrolidin-1-yl)-6-**oxo-hexanoyl**) pyrrolidine-2-carboxylic acid (CPHPC), 4,6-pyruvate acetyl of beta-D-galactopyranose, ethanolamine, phosphoethanolamine, anti-**SAP** antibody or its fragment. In (M2), the agent comprises potential drug and biological fluid from a patient. Preferred Wound Dressing: (I) further comprises high EEO agarose and cation. (I) further comprises 1 weight/volume% of high EEO agarose and 5 mM CaCl2. (I) further comprises phosphoethanolamine, Ca2+ and additional wound healing factor. The additional wound-healing factor is chosen from IL-4, IL-13, fibroblast growth factor (FGF), transforming growth factor (TGF)-beta and its combination. (I) comprises IL-13 or IL-14 at a concentration of 0.1-10 ng/ml. ACTIVITY - Vulnerary; Antidiabetic; Antiulcer. MECHANISM OF ACTION - Suppressor of **SAP** activity; Suppressor of differentiation of monocyte (claimed); Angiogenesis stimulator. To test the effects of calcium/agarose bandage on wound healing, the following test was done. About 4 cm wounds through the entire thickness of skin were made on the back of three

anesthetized rats. One rat was treated only with 4X4 gauze bandage (Topper 4X4 sponge gauze, Johnson and Johnson, Skillman, NJ) lightly soaked with 1 ml saline solution (0.9 sodium chloride weight/volume% in water). The second rat was treated with a similar bandage, with the first layer lightly soaked (1 ml) with saline/5 mM CaCl2. The third rat was treated with agarose/CaCl2 bandage. Each rat was separately anesthetized, photographed and bandaged to minimize the differences in time between anesthetizing, wounding and bandaging. After 24 hours, the rats were lightly anesthetized and weighed, then the bandages were removed and the wounds were photographed. New bandages of the same initial composition were then reapplied to each of the rats. After another 24 hours, the above process was repeated. The results showed that the rat treated with agarose/CaCl2 bandage showed considerably more rapid wound healing than either of the other two rats. USE - (M1) is useful for promoting wound healing in mammal e.g., human, or for increasing number of fibrocytes present in sample (claimed). (M1) is useful for tissue engineering, for inducing angiogenesis in regions that are in need of new vasculature, for cosmetic surgery applications, or for treating patients suffering from lacerations, diabetic complications e.g., ulcers, pressure ulcers or open fractures. ADMINISTRATION - 0.15-15 mg/kg/day of R-1-(6-(R-2-carboxy-pyrrolidin-1-yl)-**6-oxo-hexanoyl**) pyrrolidine-2-carboxylic acid (CPHPC) is administered to a mammal (claimed), by local, topical or systemic route. (65 pages)

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